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[Continued on next page]

(54) Title: COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF OVARIAN CANCER

11729.1 contg

11729-45.21.21.cons1

11729-45.21.21.cons2

11731.1contig

TCTTTTTCTTTCGATTTCCTTCAATTTGTCACGTTTGATTTTATGAAGTTGTTCAAGGCCTAACTGCTGTGTAT
TATAGCTTTCTCTGAGTTCCTTCAGCTGATTGTTAAATGAATCCATTTCTGAGAGCTTAGATGCAGTTCTTTT
ICAAGAGCATCTAATTGTTCTTTAGTCTTTGGCATAATTCTTCCTTTTTCTTATGACTTTATAGAATAAACTA
GATCCCTGAAATCAGGTGTTACTGAGCTGCATGTTTTTAATTCTTTTGGTTTAATAGCTGCTTCTCAGGGACCA
GATAGATAAGCTTATTTTGATATTCCTTAAGCTCTTGTTGAAGTTGTTTGATTTCCATAATTTCCAGGTCACAC
TGTTTATCCAAAACTTCTAGCTCAGTCTTTGTGTTTGGTTTGGACATCTTGTAGTCTGGACATAC
CTGCTGATGXTTTCCAATCACTGCTTCCAGTTCCAGGTGGAGACTTTXCTTTCTGGAGCTCAGCCTGACAATGC
CTTCTTGXTCCCCTT

(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as ovarian cancer, are disclosed. Compositions may comprise one or more ovarian carcinoma proteins, immunogenic portions thereof, polynucleotides that encode such portions or antibodies or immune system cells specific for such proteins. Such compositions may be used, for example, for the prevention and treatment of diseases such as ovarian cancer. Methods are further provided for identifying tumor antigens that are secreted from ovarian carcinomas and/or other tumors. Polypeptides and polynucleotides as provided herein may further be used

for the diagnosis and monitoring of ovarian cancer.

VO 02/06317 A2



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COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF OVARIAN CANCER

Technical Field

The present invention relates generally to ovarian cancer therapy. The invention is more specifically related to polypeptides comprising at least a portion of an ovarian carcinoma protein, and to polynucleotides encoding such polypeptides, as well as antibodies and immune system cells that specifically recognize such polypeptides. Such polypeptides, polynucleotides, antibodies and cells may be used in vaccines and pharmaceutical compositions for treatment of ovarian cancer.

10 Background of the Invention

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Ovarian cancer is a significant health problem for women in the United States and throughout the world. Although advances have been made in detection and therapy of this cancer, no vaccine or other universally successful method for prevention or treatment is currently available. Management of the disease currently relies on a combination of early diagnosis and aggressive treatment, which may include one or more of a variety of treatments such as surgery, radiotherapy, chemotherapy and hormone therapy. The course of treatment for a particular cancer is often selected based on a variety of prognostic parameters, including an analysis of specific tumor markers. However, the use of established markers often leads to a result that is difficult to interpret, and high mortality continues to be observed in many cancer patients.

Immunotherapies have the potential to substantially improve cancer treatment and survival. Such therapies may involve the generation or enhancement of an immune response to an ovarian carcinoma antigen. However, to date, relatively few ovarian carcinoma antigens are known and the generation of an immune response against such antigens has not been shown to be therapeutically beneficial.

Accordingly, there is a need in the art for improved methods for identifying ovarian tumor antigens and for using such antigens in the therapy of ovarian cancer. The present invention fulfills these needs and further provides other related advantages.

SUMMARY OF THE INVENTION

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Briefly stated, this invention provides compositions and methods for the therapy of cancer, such as ovarian cancer. In one aspect, the present invention provides polypeptides comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished. Within certain embodiments, the ovarian carcinoma protein comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of SEQ ID NO:456-457, 460-477 and 512-570 and complements of such polynucleotides.

The present invention further provides polynucleotides that encode a polypeptide as described above or a portion thereof, expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

The present invention further provides polypeptide compositions comprising an amino acid sequence selected from the group consisting of sequences recited in SEQ ID Nos:394-455, 458-459, 478-511, and 571-596.

Within other aspects, the present invention provides pharmaceutical compositions and vaccines. Pharmaceutical compositions may comprise a physiologically acceptable carrier or excipient in combination with one or more of: (i) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma proteinspecific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570 or (ii) a polynucleotide encoding such a polypeptide; (iii) an antibody that specifically binds to such a polypeptide; (iv) an antigen-presenting cell that expresses such a polypeptide and/or (v) a T cell that specifically reacts with such a polypeptide. Vaccines may comprise a non-specific immune response enhancer in combination with one or more of: (i) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions

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and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence set forth in SEQ ID Nos:394-455, 458-459, 478-511, and 571-596 or an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570 or (ii) a polynucleotide encoding such a polypeptide; (iii) an anti-idiotypic antibody that is specifically bound by an antibody that specifically binds to such a polypeptide; (iv) an antigen-presenting cell that expresses such a polypeptide and/or (v) a T cell that specifically reacts with such a polypeptide.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

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Within related aspects, pharmaceutical compositions comprising a fusion protein or polynucleotide encoding a fusion protein in combination with a physiologically acceptable carrier are provided.

Vaccines are further provided, within other aspects, comprising a fusion protein or polynucleotide encoding a fusion protein in combination with a non-specific immune response enhancer.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition or vaccine as recited above.

The present invention further provides, within other aspects, methods for stimulating and/or expanding T cells, comprising contacting T cells with (a) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence set forth in SEQ ID Nos:394-455, 458-459, 478-511, and 571-596 or an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570; (b) a polynucleotide encoding such a polypeptide and/or (c) an antigen presenting cell that

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WO 02/06317

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PCT/US01/22635

expresses such a polypeptide under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Such polypeptide, polynucleotide and/or antigen presenting cell(s) may be present within a pharmaceutical composition or vaccine, for use in stimulating and/or expanding T cells in a mammal.

Within other aspects, the present invention provides methods for inhibiting the development of ovarian cancer in a patient, comprising administering to a patient T cells prepared as described above.

Within further aspects, the present invention provides methods for inhibiting the development of ovarian cancer in a patient, comprising the steps of: (a) incubating CD4⁺ and/or CD8⁺ T cells isolated from a patient with one or more of: (i) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570; (ii) a polynucleotide encoding such a polypeptide; or (iii) an antigen-presenting cell that expresses such a polypeptide; such that T cells proliferate; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of ovarian cancer in the patient. The proliferated cells may be cloned prior to administration to the patient.

The present invention also provides, within other aspects, methods for identifying secreted tumor antigens. Such methods comprise the steps of: (a) implanting tumor cells in an immunodeficient mammal; (b) obtaining serum from the immunodeficient mammal after a time sufficient to permit secretion of tumor antigens into the serum; (c) immunizing an immunocompetent mammal with the serum; (d) obtaining antiserum from the immunocompetent mammal; and (e) screening a tumor expression library with the antiserum, and therefrom identifying a secreted tumor antigen. A preferred method for identifying a secreted ovarian carcinoma antigen comprises the steps of: (a) implanting ovarian carcinoma cells in a SCID mouse; (b) obtaining serum from the SCID mouse after a time sufficient to permit secretion of

ovarian carcinoma antigens into the serum; (c) immunizing an immunocompetent mouse with the serum; (d) obtaining antiserum from the immunocompetent mouse; and (e) screening an ovarian carcinoma expression library with the antiserum, and therefrom identifying a secreted ovarian carcinoma antigen.

The present invention also discloses antibody epitopes recognized by the O8E polyclonal anti-sera which epitopes are presented herein as SEQ ID NO: 394-415.

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Further disclosed by the present invention are 10-mer and 9-mer peptides predicted to bind HLA-0201 which peptides are disclosed herein as SEQ ID NO:416-435 and SEQ ID NO:436-455, respectively.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

In another aspect of the present invention, the applicants have unexpectedly identified a series of novel repeating sequence elements in the 5' end of the gene encoding O772P. Therefore, the present invention provides O772P polypeptides having structures represented by X_n -Y, wherein X comprises a sequence having at least 50% identity, preferably at least 70% identity, and more preferably at least 90% identity with an O772P repeat sequence set forth in SEQ ID NO: 596. Y will typically comprise a sequence having at least 80% identity, preferably at least 90% identity and more preferably at least 95% identity with the O772P constant region sequence set forth in SEQ ID NO: 594. According to this embodiment, n will generally be an integer from 1 to 35, preferably an integer from 15 to 25, and X can be the same or different.

In one preferred embodiment, X comprises a sequence selected from the group consisting of any one of SEQ ID NOs: 574-593 and Y comprises the sequence set forth in SEQ ID NO: 594.

In another preferred embodiment, an illustrative O772P polypeptide comprises the sequence set forth in SEQ ID NO: 595, containing 20 repeating sequence elements (i.e., X_{20}) wherein the X elements are arranged in the following order (moving from N-terminal to C-terminal in the O772P repeat region): SEQ ID NO: 574 - SEQ ID

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NO: 575 - SEQ ID NO: 576 - SEQ ID NO: 577 - SEQ ID NO: 578 - SEQ ID NO: 579 - SEQ ID NO: 580 - SEQ ID NO: 581 - SEQ ID NO: 582 - SEQ ID NO: 583 - SEQ ID NO: 584 - SEQ ID NO: 585 - SEQ ID NO: 586 - SEQ ID NO: 587 - SEQ ID NO: 588 - SEQ ID NO: 589 - SEQ ID NO: 590 - SEQ ID NO: 591 - SEQ ID NO: 592 - SEQ ID NO: 593.

According to another aspect of the present invention, an O772P polynucleotide is provided having the structure X_n -Y, wherein X comprises an O772P repeat sequence element selected from the group consisting of any one of SEQ ID NOs: 512-540, 542-546 and 548-567. Y will generally comprise a sequence having at least 80% identity, preferably at least 90% identity, and more preferably at least 95% identity with the O772P constant region sequence set forth in SEQ ID NO: 568. In this embodiment, n is typically an integer from 1 to 35, preferably from 15 to 25 and X can be the same or different.

In another embodiment, an illustrative O772P polynucleotide comprises the sequence set forth in SEQ ID NO: 569, containing 20 repeating sequence elements (i.e., X₂₀).

According to another aspect of the present invention, O772 polypeptides are provided comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 490-511.

According to another aspect of the present invention, O8E polypeptides are provided comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 394-415.

BRIEF DESCRIPTION OF THE SEQUENCE IDENTIFIERS AND DRAWINGS

SEQ ID NO:1-71 are ovarian carcinoma antigen polynucleotides shown 25 in Figures 1A-1S.

SEQ ID NO:72-74 are ovarian carcinoma antigen polynucleotides shown in Figures 2A-2C.

SEQ ID NO:75 is the ovarian carcinoma polynucleotide 3g (Figure 4).

SEQ ID NO:76 is the ovarian carcinoma polynucleotide 3f (Figure 5).

30 SEQ ID NO:77 is the ovarian carcinoma polynucleotide 6b (Figure 6).

SEQ ID NO:78 is the ovarian carcinoma polynucleotide 8e (Figure 7A).

SEQ ID NO:79 is the ovarian carcinoma polynucleotide 8h (Figure 7B).

SEQ ID NO:80 is the ovarian carcinoma polynucleotide 12e (Figure 8).

SEQ ID NO:81 is the ovarian carcinoma polynucleotide 12h (Figure 9).

SEQ ID NO:82-310 are ovarian carcinoma antigen polynucleotides shown in Figures 15A-15EEE.

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SEQ ID NO:311 is a full length sequence of ovarian carcinoma polynucleotide O772P.

SEQ ID NO:312 is the O772P amino acid sequence.

SEQ ID NO:313-384 are ovarian carcinoma antigen polynucleotides.

SEQ ID NO:385 represents the cDNA sequence of a form of the clone O772P, designated 21013.

SEQ ID NO:386 represents the cDNA sequence of a form of the clone O772P, designated 21003.

SEQ ID NO:387 represents the cDNA sequence of a form of the clone O772P, designated 21008.

SEQ ID NOs:388 is the amino acid sequence corresponding to SEQ ID NO:385.

SEQ ID NOs:389 is the amino acid sequence corresponding to SEQ ID NO:386.SEQ ID NOs:390 is the amino acid sequence corresponding to SEQ ID NO:387.

SEQ ID NO:391 is a full length sequence of ovarian carcinoma polynucleotide O8E.

SEQ ID NO:392-393 are protein sequences encoded by O8E.

SEQ ID NO:394-415 are peptide sequences corresponding to the OE8 antibody epitopes.

SEQ ID NO:416-435 are potential HLA-A2 10-mer binding peptides predicted using the full length open-reading frame from OE8.

SEQ ID NO:436-455 are potential HLA-A2 9-mer binding peptides 30 predicted using the full length open-reading frame from OE8.

SEQ ID NO:456 is a truncated nucleotide sequence of the full length Genbank sequence showing homology to O772P

SEQ ID NO:457 is the full length Genbank sequence showing significant homology to O772P

SEQ ID NO:458 is a protein encoding a truncated version of the full length Genbank sequence showing homology to O772P

SEQ ID NO:459 is the full length protein sequence from Genbank showing significant homology to the protein sequence for O772P

SEQ ID NO:460 encodes a unique N-terminal portion of O772P 10 contained in residues 1-70.

SEQ ID NO:461 contains unique sequence and encodes residues 1-313 of SEQ ID NO: 456.

SEQ ID NO:462 is the hypothetical sequence for clone O772P.

SEQ ID NO:463 is the cDNA sequence for clone FLJ14303.

15 SEQ ID NO:464 is a partial cDNA sequence for clone O772P.

SEQ ID NO:465 is a partial cDNA sequence for clone O772P.

SEQ ID NO:466 is a partial cDNA sequence for clone O772P.

SEQ ID NO:467 is a partial cDNA sequence for clone O772P.

SEQ ID NO:468 is a partial cDNA sequence for clone O772P.

SEQ ID NO:469 is a partial cDNA sequence for clone O772P.

SEQ ID NO:470 is a partial cDNA sequence for clone O772P.

SEQ ID NO:471 is a partial cDNA sequence for clone O772P.

SEQ ID NO:472 is a partial cDNA sequence for clone O772P.

SEQ ID NO:473 is a partial cDNA sequence for clone O772P.

SEQ ID NO:474 is a partial cDNA sequence for clone O772P.

SEQ ID NO:475 is a partial cDNA sequence for clone O772P.

SEQ ID NO:476 is a partial cDNA sequence for clone O772P.

SEQ ID NO:477 represents the novel 5'-end of the ovarian tumor antigen

O772P.

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SEQ ID NO:478 is the amino acid sequence encoded by SEQ ID NO:462.

SEQ ID NO:479 is the amino acid sequence encoded by SEQ ID NO:463.

SEQ ID NO:480 is a partial amino acid sequence encoded by SEQ ID NO:472.

5 SEQ ID NO:481 is a partial amino acid sequence encoded by a possible open reading frame of SEQ ID NO:471.

SEQ ID NO:482 is a partial amino acid sequence encoded by a second possible open reading frame of SEQ ID NO:471.

SEQ ID NO:483 is a partial amino acid sequence encoded by SEQ ID NO:467.

SEQ ID NO:484 is a partial amino acid sequence encoded by a possible open reading frame of SEQ ID NO:466.

SEQ ID NO:485 is a partial amino acid sequence encoded by a second possible open reading frame of SEQ ID NO:466.

SEQ ID NO:486 is a partial amino acid sequence encoded by SEQ ID NO:465.

SEQ ID NO:487 is a partial amino acid sequence encoded by SEQ ID NO:464.

SEQ ID NO:488 represents the extracellular, transmembrane and 20 cytoplasmic regions of O772P.

SEQ ID NO:489 represents the predicted extracellular domain of O772P.

SEQ ID NO:490 represents the amino acid sequence of peptide #2 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:491 represents the amino acid sequence of peptide #6 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:492 represents the amino acid sequence of peptide #7 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:493 represents the amino acid sequence of peptide #8 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:494 represents the amino acid sequence of peptide #9 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:495 represents the amino acid sequence of peptide #11 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:496 represents the amino acid sequence of peptide #13 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:497 represents the amino acid sequence of peptide #22 which corresponds to an O772P specific antibody epitope.

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SEQ ID NO:498 represents the amino acid sequence of peptide #24 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:499 represents the amino acid sequence of peptide #27 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:500 represents the amino acid sequence of peptide #40 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:501 represents the amino acid sequence of peptide #41 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:502 represents the amino acid sequence of peptide #47 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:503 represents the amino acid sequence of peptide #50 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:504 represents the amino acid sequence of peptide #51 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:505 represents the amino acid sequence of peptide #52 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:506 represents the amino acid sequence of peptide #53 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:507 represents the amino acid sequence of peptide #58 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:508 represents the amino acid sequence of peptide #59 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:509 represents the amino acid sequence of peptide #60 which corresponds to an O772P specific antibody epitope.

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SEQ ID NO:510 represents the amino acid sequence of peptide #61 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:511 represents the amino acid sequence of peptide #71 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:512 (O772P repeat1) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:513 (O772P repeat2) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:514 (O772P repeat3) represents an example of a cDNA sequence corresponding to repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:515 (O772P repeat4) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:516 (O772P repeat5) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:517 (HB repeat1) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:518 (HB repeat2) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:519 (HB repeat3) represents an example of a cDNA sequence corresponding to repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:520 (HB repeat4) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:521 (HB repeat5) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:522 (HB repeat6 5'-end) represents an example of a cDNA sequence corresponding to repeat number 16 from the 5' variable region of O772P.

SEQ ID NO:523 (1043400.1 repeat1) represents an example of a cDNA sequence corresponding to repeat number 9 from the 5' variable region of O772P.

SEQ ID NO:524 (1043400.1 repeat2) represents an example of a cDNA sequence corresponding to repeat number 10 from the 5' variable region of O772P.

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SEQ ID NO:525 (1043400.1 repeat3) represents an example of a cDNA sequence corresponding to repeat number 10/11 from the 5' variable region of O772P. SEQ ID NO:526 (1043400.1 repeat4) represents an example of a cDNA sequence corresponding to repeat number 11 from the 5' variable region of O772P. SEQ ID NO:527 (1043400.1 repeat5) represents an example of a cDNA sequence corresponding to repeat number 14 from the 5' variable region of O772P. SEQ ID NO:528 (1043400.1 repeat6) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P. SEQ ID NO:529 (1043400.3 repeat1) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P. SEQ ID NO:530 (1043400.3 repeat2) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P. SEQ ID NO:531 (1043400.5 repeat1) represents an example of a cDNA sequence corresponding to repeat number 8 from the 5' variable region of O772P. SEQ ID NO:532 (1043400.5 repeat2) represents an example of a cDNA sequence corresponding to repeat number 9 from the 5' variable region of O772P, in addition containing intron sequence. SEQ ID NO:533 (1043400.5 repeat2) represents an example of a cDNA sequence corresponding to repeat number 9 from the 5' variable region of O772P. SEQ ID NO:534 (1043400.8 repeat1) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:535 (1043400.8 repeat2) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:536 (1043400.8 repeat3) represents an example of a cDNA sequence corresponding to repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:537 (1043400.9 repeat1) represents an example of a cDNA sequence corresponding to repeat number 4 from the 5' variable region of O772P.

SEQ ID NO:538 (1043400.9 repeat2) represents an example of a cDNA sequence corresponding to repeat number 5 from the 5' variable region of O772P.

SEQ ID NO:539 (1043400.9 repeat3) represents an example of a cDNA sequence corresponding to repeat number 7 from the 5' variable region of O772P.

SEQ ID NO:540 (1043400.9 repeat4) represents an example of a cDNA sequence corresponding to repeat number 8 from the 5' variable region of O772P.

SEQ ID NO:541 (1043400.11 repeat1) represents an example of a cDNA sequence corresponding to repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:542 (1043400.11 repeat2) represents an example of a cDNA sequence corresponding to repeat number 2 from the 5' variable region of O772P.

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SEQ ID NO:543 (1043400.11 repeat3) represents an example of a cDNA sequence corresponding to repeat number 3 from the 5' variable region of O772P.

SEQ ID NO:544 (1043400.11 repeat4) represents an example of a cDNA sequence corresponding to repeat number 11 from the 5' variable region of O772P.

SEQ ID NO:545 (1043400.11 repeat5) represents an example of a cDNA sequence corresponding to repeat number 12 from the 5' variable region of O772P.

SEQ ID NO:546 (1043400.12 repeat1) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:547 (PB repeatA) represents an example of a cDNA sequence corresponding to repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:548 (PB repeatB) represents an example of a cDNA sequence corresponding to repeat number 2 from the 5' variable region of O772P.

SEQ ID NO:549 (PB repeatE) represents an example of a cDNA sequence corresponding to repeat number 3 from the 5' variable region of O772P.

SEQ ID NO:550 (PB repeatG) represents an example of a cDNA sequence corresponding to repeat number 4 from the 5' variable region of O772P.

SEQ ID NO:551 (PB repeatC) represents an example of a cDNA sequence corresponding to repeat number 4 from the 5' variable region of O772P.

SEQ ID NO:552 (PB repeatH) represents an example of a cDNA sequence corresponding to repeat number 6 from the 5' variable region of O772P.

SEQ ID NO:553 (PB repeatJ) represents an example of a cDNA sequence corresponding to repeat number 7 from the 5' variable region of O772P.

SEQ ID NO:554 (PB repeatK) represents an example of a cDNA sequence corresponding to repeat number 8 from the 5' variable region of O772P.

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SEQ ID NO:555 (PB repeatD) represents an example of a cDNA sequence corresponding to repeat number 9 from the 5' variable region of O772P.

SEQ ID NO:556 (PB repeatI) represents an example of a cDNA sequence corresponding to repeat number 10 from the 5' variable region of O772P.

SEQ ID NO:557 (PB repeatM) represents an example of a cDNA sequence corresponding to repeat number 11 from the 5' variable region of O772P.

SEQ ID NO:558 (PB repeat9) represents an example of a cDNA sequence corresponding to repeat number 12 from the 5' variable region of O772P.

SEQ ID NO:559 (PB repeat8.5) represents an example of a cDNA sequence corresponding to repeat number 13 from the 5' variable region of O772P.

SEQ ID NO:560 (PB repeat8) represents an example of a cDNA sequence corresponding to repeat number 14 from the 5' variable region of O772P.

SEQ ID NO:561 (PB repeat7) represents an example of a cDNA sequence corresponding to repeat number 15 from the 5' variable region of O772P.

SEQ ID NO:562 (PB repeat6) represents an example of a cDNA sequence corresponding to repeat number 16 from the 5' variable region of O772P.

SEQ ID NO:563 (PB repeat5) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:564 (PB repeat4) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:565 (PB repeat3) represents an example of a cDNA sequence corresponding to repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:566 (PB repeat2) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:567 (PB repeat1) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:568 represents the cDNA sequence form the 3' constant region.

SEQ ID NO:569 represents a cDNA sequence containing the consensus sequences of the 21 repeats, the 3' constant region and the 3' untranslated region.

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SEQ ID NO:570 represents the cDNA sequence of the consensus repeat sequence.

SEQ ID NO:571 represents the consensus amino acid sequence of one potential open reading frame of repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:572 represents the consensus amino acid sequence of a second potential open reading frame of repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:573 represents the consensus amino acid sequence of a third potential open reading frame of repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:574 represents the consensus amino acid sequence of repeat number 2 from the 5' variable region of O772P.

SEQ ID NO:575 represents the consensus amino acid sequence of repeat number 3 from the 5' variable region of O772P.

SEQ ID NO:576 represents the consensus amino acid sequence of repeat number 4 from the 5' variable region of O772P.

SEQ ID NO:577 represents the consensus amino acid sequence of repeat number 5 from the 5' variable region of O772P.

SEQ ID NO:578 represents the consensus amino acid sequence of repeat number 6 from the 5' variable region of O772P.

SEQ ID NO:579 represents the consensus amino acid sequence of repeat number 7 from the 5' variable region of O772P.

SEQ ID NO:580 represents the consensus amino acid sequence of repeat number 8 from the 5' variable region of O772P.

SEQ ID NO:581 represents the consensus amino acid sequence of repeat number 9 from the 5' variable region of O772P.

SEQ ID NO:582 represents the consensus amino acid sequence of repeat number 10 from the 5' variable region of O772P.

SEQ ID NO:583 represents the consensus amino acid sequence of repeat number 11 from the 5' variable region of O772P.

30 SEQ ID NO:584 represents the consensus amino acid sequence of repeat number 12 from the 5' variable region of O772P.

SEQ ID NO:585 represents the consensus amino acid sequence of repeat number 13 from the 5' variable region of O772P.

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SEQ ID NO:586 represents the consensus amino acid sequence of repeat number 14 from the 5' variable region of O772P.

5 SEQ ID NO:587 represents the consensus amino acid sequence of repeat number 15 from the 5' variable region of O772P.

SEQ ID NO:588 represents the consensus amino acid sequence of repeat number 16 from the 5' variable region of O772P.

SEQ ID NO:589 represents the consensus amino acid sequence of repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:590 represents the consensus amino acid sequence of repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:591 represents the consensus amino acid sequence of repeat number 19 from the 5' variable region of O772P.

15 SEQ ID NO:592 represents the consensus amino acid sequence of repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:593 represents the consensus amino acid sequence of repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:594 represents the amino acid sequence of the 3' constant 20 region.

SEQ ID NO:595 represents an amino acid sequence containing the consensus sequences of the 21 repeats and the 3' constant region.

SEQ ID NO:596 represents the amino acid sequence of the consensus repeat sequence.

Figures 1A-1S (SEQ ID NO:1-71) depict partial sequences of polynucleotides encoding representative secreted ovarian carcinoma antigens.

Figure 2A-2C depict full insert sequences for three of the clones of Figure 1. Figure 2A shows the sequence designated O7E (11731; SEQ ID NO:72), Figure 2B shows the sequence designated O9E (11785; SEQ ID NO:73) and Figure 2C shows the sequence designated O8E (13695; SEQ ID NO:74).

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Figure 3 presents results of microarray expression analysis of the ovarian carcinoma sequence designated O8E.

Figure 4 presents a partial sequence of a polynucleotide (designated 3g; SEQ ID NO:75) encoding an ovarian carcinoma sequence that is a splice fusion between the human T-cell leukemia virus type I oncoprotein TAX and osteonectin.

Figure 5 presents the ovarian carcinoma polynucleotide designated 3f (SEQ ID NO:76).

Figure 6 presents the ovarian carcinoma polynucleotide designated 6b (SEQ ID NO:77).

Figures 7A and 7B present the ovarian carcinoma polynucleotides designated 8e (SEQ ID NO:78) and 8h (SEQ ID NO:79).

Figure 8 presents the ovarian carcinoma polynucleotide designated 12c (SEQ ID NO:80).

Figure 9 presents the ovarian carcinoma polynucleotide designated 12h (SEQ ID NO:81).

Figure 10 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 3f.

Figure 11 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 6b.

Figure 12 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 8e.

Figure 13 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 12c.

Figure 14 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 12h.

Figures 15A-15EEE depict partial sequences of additional polynucleotides encoding representative secreted ovarian carcinoma antigens (SEQ ID NO:82-310).

Figure 16 is a diagram illustrating the location of various partial O8E sequences within the full length sequence.

WO 02/06317

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Figure 17 is a graph illustrating the results of epitope mapping studies on O8E protein.

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Figure 18 is graph of a fluorescence activated cell sorting (FACS) analysis of O8E cell surface expression.

Figure 19 is graph of a FACS analysis of O8E cell surface expression.

PCT/US01/22635

Figure 20 shows FACS analysis results for O8E transfected HEK293 cells demonstrating cell surface expression of O8E.

Figure 21 shows FACS analysis results for SKBR3 breast tumor cells demonstrating cell surface expression of O8E.

Figure 22 shows 08E expression in HEK 293 cells. The cells were probed with anti-08E rabbit polyclonal antisera #2333L.

Figure 23 shows the ELISA analysis of anti-08E rabbit sera.

Figure 24 shows the ELISA analysis of affinity purified rabbit anti-08E polyclonal antibody.

Figure 25 is a graph determining antibody internalization of anti-O8E mAb showing that mAbs against amino acids 61-80 induces ligand internalization.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy of cancer, such as ovarian cancer. The compositions described herein may include immunogenic polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies that bind to a polypeptide, antigen presenting cells (APCs) and/or immune system cells (e.g., T cells).

Polypeptides of the present invention generally comprise at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof. Certain ovarian carcinoma proteins have been identified using an immunoassay technique, and are referred to herein as ovarian carcinoma antigens. An "ovarian carcinoma antigen" is a protein that is expressed by ovarian tumor cells (preferably human cells) at a level that is at least two fold higher than the level in normal ovarian cells. Certain ovarian carcinoma antigens react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera generated against serum from an immunodeficient animal

PCT/US01/22635

implanted with a human ovarian tumor. Such ovarian carcinoma antigens are shed or secreted from an ovarian tumor into the sera of the immunodeficient animal. Accordingly, certain ovarian carcinoma antigens provided herein are secreted antigens. Certain nucleic acid sequences of the subject invention generally comprise a DNA or RNA sequence that encodes all or a portion of such a polypeptide, or that is complementary to such a sequence.

The present invention further provides ovarian carcinoma sequences that are identified using techniques to evaluate altered expression within an ovarian tumor. Such sequences may be polynucleotide or protein sequences. Ovarian carcinoma sequences are generally expressed in an ovarian tumor at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in normal ovarian tissue, as determined using a representative assay provided herein. Certain partial ovarian carcinoma polynucleotide sequences are presented herein. Proteins encoded by genes comprising such polynucleotide sequences (or complements thereof) are also considered ovarian carcinoma proteins.

Antibodies are generally immune system proteins, or antigen-binding fragments thereof, that are capable of binding to at least a portion of an ovarian carcinoma polypeptide as described herein. T cells that may be employed within the compositions provided herein are generally T cells (e.g., CD4⁺ and/or CD8⁺) that are specific for such a polypeptide. Certain methods described herein further employ antigen-presenting cells (such as dendritic cells or macrophages) that express an ovarian carcinoma polypeptide as provided herein.

Ovarian Carcinoma Polynucleotides

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Any polynucleotide that encodes an ovarian carcinoma protein or a portion or other variant thereof as described herein is encompassed by the present invention. Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at least 30 consecutive nucleotides, and more preferably at least 45 consecutive nucleotides, that encode a portion of an ovarian carcinoma protein. More preferably, a polynucleotide encodes an immunogenic portion of an ovarian carcinoma protein, such as an ovarian carcinoma antigen. Polynucleotides complementary to any

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PCT/US01/22635

such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (i.e., an endogenous sequence that encodes an ovarian carcinoma protein or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native ovarian carcinoma protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native ovarian carcinoma protein or a portion thereof.

The percent identity for two polynucleotide or polypeptide sequences may be readily determined by comparing sequences using computer algorithms well known to those of ordinary skill in the art, such as Megalign, using default parameters. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, or 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Optimal alignment of sequences for comparison may be conducted, for example, using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. Preferably, the percentage of sequence identity is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the window may comprise additions or deletions (i.e., gaps) of 20 % or less, usually 5 to 15 %, or 10 to 12%, relative to the reference sequence (which does not contain additions or

21

deletions). The percent identity may be calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e., the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding a native ovarian carcinoma protein (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

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It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Polynucleotides may be prepared using any of a variety of techniques. For example, an ovarian carcinoma polynucleotide may be identified, as described in more detail below, by screening a late passage ovarian tumor expression library with antisera generated against sera of immunocompetent mice after injection of such mice with sera from SCID mice implanted with late passage ovarian tumors. Ovarian carcinoma polynucleotides may also be identified using any of a variety of techniques designed to evaluate differential gene expression. Alternatively, polynucleotides may

WO 02/06317

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PCT/US01/22635

be amplified from cDNA prepared from ovarian tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion may be used to isolate a full length gene from a suitable library (e.g., an ovarian carcinoma cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with ³²P) using well known techniques. A bacterial or bacteriophage library is then screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences are then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target

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sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

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One such amplification technique is inverse PCR (see Triglia et al., Nucl. Acids Res. 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Additional techniques include capture PCR (Lagerstrom et al., PCR Methods Applic. 1:111-19, 1991) and walking PCR (Parker et al., Nucl. Acids. Res. 19:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence.

Certain nucleic acid sequences of cDNA molecules encoding portions of ovarian carcinoma antigens are provided in Figures 1A-1S (SEQ ID NO:1 to 71) and Figures 15A to 15EEE (SEQ ID NO:82 to 310). The sequences provided in Figures 1A-1S appear to be novel. For sequences in Figures 15A-15EEE, database searches revealed matches having substantial identity. These polynucleotides were isolated by serological screening of an ovarian tumor cDNA expression library, using a technique designed to identify secreted tumor antigens. Briefly, a late passage ovarian tumor expression library was prepared from a SCID-derived human ovarian tumor (OV9334) in the vector λ-screen (Novagen). The sera used for screening were obtained by

injecting immunocompetent mice with sera from SCID mice implanted with one late passage ovarian tumors. This technique permits the identification of cDNA molecules that encode immunogenic portions of secreted tumor antigens.

The polynucleotides recited herein, as well as full length polynucleotides comprising such sequences, other portions of such full length polynucleotides, and sequences complementary to all or a portion of such full length molecules, are specifically encompassed by the present invention. It will be apparent to those of ordinary skill in the art that this technique can also be applied to the identification of antigens that are secreted from other types of tumors.

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Other nucleic acid sequences of cDNA molecules encoding portions of ovarian carcinoma proteins are provided in Figures 4-9 (SEQ ID NO:75-81), as well as SEQ ID NO:313-384. These sequences were identified by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least five fold greater in an ovarian tumor than in normal ovarian tissue, as determined using a representative assay provided herein). Such screens were performed using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). SEQ ID NO:311 and 391 provide full length sequences incorporating certain of these nucleic acid sequences.

Any of a variety of well known techniques may be used to evaluate tumor-associated expression of a cDNA. For example, hybridization techniques using labeled polynucleotide probes may be employed. Alternatively, or in addition, amplification techniques such as real-time PCR may be used (see Gibson et al., Genome Research 6:995-1001, 1996; Heid et al., Genome Research 6:986-994, 1996). Real-time PCR is a technique that evaluates the level of PCR product accumulation during amplification. This technique permits quantitative evaluation of mRNA levels in multiple samples. Briefly, mRNA is extracted from tumor and normal tissue and cDNA is prepared using standard techniques. Real-time PCR may be performed, for example, using a Perkin Elmer/Applied Biosystems (Foster City, CA) 7700 Prism instrument. Matching primers and fluorescent probes may be designed for genes of interest using, for example, the primer express program provided by Perkin Elmer/Applied Biosystems

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(Foster City, CA). Optimal concentrations of primers and probes may be initially determined by those of ordinary skill in the art, and control (e.g., β-actin) primers and probes may be obtained commercially from, for example, Perkin Elmer/Applied Biosystems (Foster City, CA). To quantitate the amount of specific RNA in a sample, a standard curve is generated alongside using a plasmid containing the gene of interest. Standard curves may be generated using the Ct values determined in the real-time PCR, which are related to the initial cDNA concentration used in the assay. Standard dilutions ranging from 10-10⁶ copies of the gene of interest are generally sufficient. In addition, a standard curve is generated for the control sequence. This permits standardization of initial RNA content of a tissue sample to the amount of control for comparison purposes.

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Polynucleotide variants may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis. Modifications in a polynucleotide sequence may also be introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (see Adelman et al., DNA 2:183, 1983). Alternatively, RNA molecules may be generated by in vitro or in vivo transcription of DNA sequences encoding an ovarian carcinoma antigen, or portion thereof, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Certain portions may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a portion may be administered to a patient such that the encoded polypeptide is generated in vivo.

A portion of a sequence complementary to a coding sequence (i.e., an antisense polynucleotide) may also be used as a probe or to modulate gene expression. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells or tissues to facilitate the production of antisense RNA. An antisense polynucleotide may be used, as described herein, to inhibit expression of an ovarian carcinoma protein. Antisense technology can be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (see Gee et al., In Huber and Carr, Molecular and Immunologic Approaches.

Futura Publishing Co. (Mt. Kisco, NY; 1994). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (e.g., promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes.

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Any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Such formulations are particularly useful for therapeutic purposes, as described below. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (e.g., avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also

PCT/US01/22635

be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

Ovarian Carcinoma Polypeptides

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Within the context of the present invention, polypeptides may comprise at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof, as described herein. As noted above, certain ovarian carcinoma proteins are ovarian carcinoma antigens that are expressed by ovarian tumor cells and react detectably within an immunoassay (such as an ELISA) with antisera generated against serum from an immunodeficient animal implanted with an ovarian tumor. Other ovarian carcinoma proteins are encoded by ovarian carcinoma polynucleotides recited herein. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of an antigen that is recognized (*i.e.*, specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of an ovarian carcinoma protein or a variant thereof. Preferred immunogenic portions are encoded by cDNA molecules isolated as described herein. Further immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with ovarian carcinoma protein-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "ovarian carcinoma protein-

specific" if they specifically bind to an ovarian carcinoma protein (*i.e.*, they react with the ovarian carcinoma protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera, antibodies and T cells may be prepared as described herein, and using well known techniques. An immunogenic portion of a native ovarian carcinoma protein is a portion that reacts with such antisera, antibodies and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length protein. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ¹²⁵I-labeled Protein A.

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As noted above, a composition may comprise a variant of a native ovarian carcinoma protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native ovarian carcinoma protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with ovarian carcinoma protein-specific antisera may be enhanced or unchanged, relative to the native ovarian carcinoma protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native ovarian carcinoma protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with ovarian carcinoma protein-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

WO 02/06317

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Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity to the native polypeptide. Preferably, a variant contains conservative substitutions. "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

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PCT/US01/22635

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells

include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

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Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Applied BioSystems, Inc. (Foster City, CA), and may be operated according to the manufacturer's instructions.

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Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises one polypeptide as described herein and a known tumor antigen, such as an ovarian carcinoma protein or a variant of such a protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused

31

protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

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A peptide linker sequence may be employed to separate the first and the second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., Gene 40:39-46, 1985; Murphy et al., Proc. Natl. Acad. Sci. USA 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. New Engl. J. Med., 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in E. coli (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen present cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

Binding Agents

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The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to an ovarian carcinoma protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to an ovarian carcinoma protein if it reacts at a detectable level (within, for example, an ELISA) with an ovarian carcinoma protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a "complex" is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10³ L/mol. The binding constant maybe determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as ovarian cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a ovarian carcinoma antigen will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological

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samples (e.g., blood, sera, leukophoresis, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the

desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

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Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ⁹⁰Y, ¹²³I, ¹²⁵I, ¹³¹I, ¹⁸⁶Re, ¹⁸⁸Re, ²¹¹At, and ²¹²Bi. Preferred drugs include

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WO 02/06317 PCT/US01/22635

methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

36

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, e.g., U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of

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WO 02/06317 PCT/US01/22635

derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

37

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

Also provided herein are anti-idiotypic antibodies that mimic an immunogenic portion of an ovarian carcinoma protein. Such antibodies may be raised against an antibody, or antigen-binding fragment thereof, that specifically binds to an

PCT/US01/22635

immunogenic portion of an ovarian carcinoma protein, using well known techniques. Anti-idiotypic antibodies that mimic an immunogenic portion of an ovarian carcinoma protein are those antibodies that bind to an antibody, or antigen-binding fragment thereof, that specifically binds to an immunogenic portion of an ovarian carcinoma protein, as described herein.

T Cells

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WO 02/06317

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for an ovarian carcinoma protein. Such cells may generally be prepared in vitro or ex vivo, using standard procedures. For example, T cells may be present within 10 (or isolated from) bone marrow, peripheral blood or a fraction of bone marrow or peripheral blood of a mammal, such as a patient, using a commercially available cell separation system, such as the CEPRATETM system, available from CellPro Inc., Bothell WA (see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human animals, cell lines or cultures.

T cells may be stimulated with an ovarian carcinoma polypeptide, polynucleotide encoding an ovarian carcinoma polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, an ovarian carcinoma polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for an ovarian carcinoma polypeptide if the T cells kill target cells coated with an ovarian carcinoma polypeptide or expressing a gene encoding such a polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., Cancer Res. 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be

accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with an ovarian carcinoma polypeptide (200 ng/ml - 100 µg/ml, preferably 100 ng/ml - 25 µg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells and/or contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-y) is indicative of T cell activation (see Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998). T cells that have been activated in response to an ovarian carcinoma polypeptide, polynucleotide or ovarian carcinoma polypeptide-expressing APC may be CD4⁺ and/or CD8⁺. Ovarian carcinoma polypeptide-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient or a related or unrelated donor and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4⁺ or CD8⁺ T cells that proliferate in response to an ovarian carcinoma polypeptide, polynucleotide or APC can be expanded in number either in vitro or in vivo. Proliferation of such T cells in vitro may be accomplished in a variety of ways. For example, the T cells can be re-exposed to an ovarian carcinoma polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize an ovarian carcinoma polypeptide. Alternatively, one or more T cells that proliferate in the presence of an ovarian carcinoma polypeptide can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution. Following expansion, the cells may be administered back to the patient as described, for example, by Chang et al., Crit. Rev. Oncol. Hematol. 22:213, 1996.

Pharmaceutical Compositions and Vaccines

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Within certain aspects, polypeptides, polynucleotides, binding agents 30 and/or immune system cells as described herein may be incorporated into

WO 02/06317

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PCT/US01/22635

pharmaceutical compositions or vaccines. Pharmaceutical compositions comprise one or more such compounds or cells and a physiologically acceptable carrier. Vaccines may comprise one or more such compounds or cells and a non-specific immune response enhancer. A non-specific immune response enhancer may be any substance that enhances an immune response to an exogenous antigen. Examples of non-specific immune response enhancers include adjuvants, biodegradable microspheres (e.g., polylactic galactide) and liposomes (into which the compound is incorporated; see e.g., Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound within the composition or vaccine.

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A pharmaceutical composition or vaccine may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated in situ. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as Bacillus-Calmette-Guerrin) that expresses an immunogenic portion of the polypeptide on its cell surface. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., PNAS 86:317-321, 1989; Flexner et al., Ann. N.Y. Acad. Sci. 569:86-103, 1989; Flexner et al., Vaccine 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, Biotechniques 6:616-627, 1988; Rosenfeld et al., Science 252:431-434, 1991; Kolls et al., PNAS 91:215-219, 1994; Kass-Eisler et al.,

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PNAS 90:11498-11502, 1993; Guzman et al., Circulation 88:2838-2848, 1993; and Guzman et al., Cir. Res. 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., Science 259:1745-1749, 1993 and reviewed by Cohen, Science 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

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While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier 10 will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. 15 For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109. 20

Such compositions may also comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide) and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of non-specific immune response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune

WO 02/06317

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responses, such as lipid A, Bortadella pertussis or Mycobacterium tuberculosis derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI), Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ), alum, biodegradable microspheres, monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the vaccines provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN-γ, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6, IL-10 and TNF-β) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, Ann. Rev. Immunol. 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Ribi ImmunoChem Research Inc. (Hamilton, MT; see US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). Also preferred is AS-2 (SmithKline Beecham). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555. Another preferred adjuvant is a saponin, preferably QS21, which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO

WO 02/06317

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PCT/US01/22635

96/33739. Other preferred formulations comprises an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210. Any vaccine provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient.

The compositions described herein may be administered as part of a sustained release formulation (i.e., a formulation such as a capsule or sponge that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and vaccines to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects per se and/or to be immunologically compatible with the receiver (i.e., matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to

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PCT/US01/22635

be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (see Timmerman and Levy, Ann. Rev. Med. 50:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate in situ, with marked cytoplasmic processes (dendrites) visible in vitro) and based on the lack of differentiation markers of B cells (CD19 and CD20), T cells (CD3), monocytes (CD14) and natural killer cells (CD56), as determined using standard assays. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells in vivo or ex vivo, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (see Zitvogel et al., Nature Med. 4:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcγ receptor, mannose receptor and DEC-205 marker. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80 and CD86).

APCs may generally be transfected with a polynucleotide encoding a ovarian carcinoma antigen (or portion or other variant thereof) such that the antigen, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place ex vivo, and a composition or vaccine comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs in vivo. In vivo and ex vivo transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., Immunology and cell Biology 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (e.g., vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (e.g., a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

Cancer Therapy

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In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as ovarian cancer. Within such 20 methods, pharmaceutical compositions and vaccines are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and vaccines may be used to prevent the development of a 25 cancer or to treat a patient afflicted with a cancer. Within certain preferred embodiments, a patient is afflicted with ovarian cancer. Such cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration 30 of radiotherapy or conventional chemotherapeutic drugs.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immuno

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response-modifying agents (such as tumor vaccines, bacterial adjuvants and/or

cytokines).

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Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T lymphocytes (such as CD8⁺ cytotoxic T lymphocytes and CD4⁺ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigenpresenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system.

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WO 02/06317 PCT/US01/22635

Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., Immunological Reviews 157:177, 1997).

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Alternatively, a vector expressing a polypeptide recited herein may be introduced into stem cells taken from a patient and clonally propagated *in vitro* for autologous transplant back into the same patient.

Routes and frequency of administration, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration), orally or in the bed of a resected tumor. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (i.e., untreated) level.. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells in vitro. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (e.g., more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 100 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical

outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to an ovarian carcinoma antigen generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

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Screens for Identifying Secreted Ovarian Carcinoma Antigens

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The present invention provides methods for identifying secreted tumor antigens. Within such methods, tumors are implanted into immunodeficient animals such as SCID mice and maintained for a time sufficient to permit secretion of tumor antigens into serum. In general, tumors may be implanted subcutaneously or within the gonadal fat pad of an immunodeficient animal and maintained for 1-9 months, preferably 1-4 months. Implantation may generally be performed as described in WO 97/18300. The serum containing secreted antigens is then used to prepare antisera in immunocompetent mice, using standard techniques and as described herein. Briefly, 50-100 µL of sera (pooled from three sets of immunodeficient mice, each set bearing a different SCID-derived human ovarian tumor) may be mixed 1:1 (vol:vol) with an appropriate adjuvant, such as RIBI-MPL or MPL + TDM (Sigma Chemical Co., St. Louis, MO) and injected intraperitoneally into syngeneic immunocompetent animals at monthly intervals for a total of 5 months. Antisera from animals immunized in such a manner may be obtained by drawing blood after the third, fourth and fifth immunizations. The resulting antiserum is generally pre-cleared of E. coli and phage antigens and used (generally following dilution, such as 1:200) in a serological expression screen.

The library is typically an expression library containing cDNAs from one or more tumors of the type that was implanted into SCID mice. This expression library may be prepared in any suitable vector, such as λ-screen (Novagen). cDNAs that encode a polypeptide that reacts with the antiserum may be identified using standard techniques, and sequenced. Such cDNA molecules may be further characterized to

evaluate expression in tumor and normal tissue, and to evaluate antigen secretion in patients.

49

The methods provided herein have advantages over other methods for tumor antigen discovery. In particular, all antigens identified by such methods should be secreted or released through necrosis of the tumor cells. Such antigens may be present on the surface of tumor cells for an amount of time sufficient to permit targeting and killing by the immune system, following vaccination.

Methods for Detecting Cancer

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In general, a cancer may be detected in a patient based on the presence of one or more ovarian carcinoma proteins and/or polynucleotides encoding such proteins in a biological sample (such as blood, sera, urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as ovarian cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of protein that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, an ovarian carcinoma-associated sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding

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agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length ovarian carcinoma proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 µg, and preferably about 100 ng to about 1 µg, is sufficient to immobilize an adequate amount of binding agent.

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PCT/US01/22635

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (i.e., incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with ovarian cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over

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WO 02/06317 PCT/US01/22635

a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

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Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20TM. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibodypolypeptide complex for an amount of time sufficient to detect the bound polypeptide.

An appropriate amount of time may generally be determined by assaying the level of
binding that occurs over a period of time. Unbound detection reagent is then removed
and bound detection reagent is detected using the reporter group. The method employed
for detecting the reporter group depends upon the nature of the reporter group. For
radioactive groups, scintillation counting or autoradiographic methods are generally
appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups
and fluorescent groups. Biotin may be detected using avidin, coupled to a different
reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme
reporter groups may generally be detected by the addition of substrate (generally for a
specific period of time), followed by spectroscopic or other analysis of the reaction
products.

To determine the presence or absence of a cancer, such as ovarian cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., Clinical Epidemiology: A Basic Science for Clinical Medicine, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%-specificity)

that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

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In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

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Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use ovarian carcinoma polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such ovarian carcinoma protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with an ovarian carcinoma protein in a biological sample. Within certain methods, a biological sample comprising CD4⁺ and/or CD8⁺ T cells isolated from a patient is incubated with an ovarian carcinoma protein, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated in vitro for 2-9 days (typically 4 days) at 37°C with an ovarian carcinoma protein (e.g., 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of ovarian carcinoma protein to serve as a control. For CD4⁺ T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8⁺ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding an ovarian carcinoma protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of an ovarian carcinoma protein cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the ovarian carcinoma protein. The amplified cDNA is then separated and detected using techniques well

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WO 02/06317 PCT/US01/22635

known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding an ovarian carcinoma protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

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To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding an ovarian carcinoma protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence provided herein. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., PCR Technology, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample such as a biopsy tissue and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, ovarian carcinoma proteins and polynucleotides encoding such proteins may be used as markers for monitoring the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide detected by the binding agent increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple ovarian carcinoma protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

Diagnostic Kits

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The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to an ovarian carcinoma protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain

57

a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding an ovarian carcinoma protein in a biological sample. Such kits generally 5 comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding an ovarian carcinoma protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding an ovarian carcinoma protein.

The following Examples are offered by way of illustration and not by way of limitation.

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EXAMPLES

EXAMPLE 1

IDENTIFICATION OF REPRESENTATIVE OVARIAN CARCINOMA PROTEIN CDNAS

This Example illustrates the identification of cDNA molecules encoding ovarian carcinoma proteins.

Anti-SCID mouse sera (generated against sera from SCID mice carrying late passage ovarian carcinoma) was pre-cleared of E. coli and phage antigens and used at a 1:200 dilution in a serological expression screen. The library screened was made from a SCID-derived human ovarian tumor (OV9334) using a directional RH oligo(dT) priming cDNA library construction kit and the λ Screen vector (Novagen). A bacteriophage lambda screen was employed. Approximately 400,000 pfu of the amplified OV9334 library were screened.

196 positive clones were isolated. Certain sequences that appear to be novel are provided in Figures 1A-1S and SEQ ID NO:1 to 71. Three complete insert sequences are shown in Figures 2A-2C (SEQ ID NO:72 to 74). Other clones having known sequences are presented in Figures 15A-15EEE (SEQ ID NO:82 to 310). Database searches identified the following sequences that were substantially identical to the sequences presented in Figures 15A-15EEE.

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These clones were further characterized using microarray technology to determine mRNA expression levels in a variety of tumor and normal tissues. Such analyses were performed using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions. PCR amplification products were arrayed on slides, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes and the slides were scanned to measure fluorescence intensity. Data was analyzed using Synteni's provided GEMtools software. The results for one clone (13695, also referred to as O8E) are shown in Figure 3.

EXAMPLE 2

IDENTIFICATION OF OVARIAN CARCINOMA CDNAs USING MICROARRAY TECHNOLOGY

This Example illustrates the identification of ovarian carcinoma polynucleotides by PCR subtraction and microarray analysis. Microarrays of cDNAs were analyzed for ovarian tumor-specific expression using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997).

A PCR subtraction was performed using a tester comprising cDNA of four ovarian tumors (three of which were metastatic tumors) and a driver of cDNA form five normal tissues (adrenal gland, lung, pancreas, spleen and brain). cDNA fragments recovered from this subtraction were subjected to DNA microarray analysis where the fragments were PCR amplified, adhered to chips and hybridized with fluorescently labeled probes derived from mRNAs of human ovarian tumors and a variety of normal human tissues. In this analysis, the slides were scanned and the fluorescence intensity was measured, and the data were analyzed using Synteni's GEMtools software. In general, sequences showing at least a 5-fold increase in expression in tumor cells (relative to normal cells) were considered ovarian tumor antigens. The fluorescent results were analyzed and clones that displayed increased expression in ovarian tumors were further characterized by DNA sequencing and database searches to determine the novelty of the sequences.

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Using such assays, an ovarian tumor antigen was identified that is a splice fusion between the human T-cell leukemia virus type I oncoprotein TAX (see Jin et al., Cell 93:81-91, 1998) and an extracellular matrix protein called osteonectin. A splice junction sequence exists at the fusion point. The sequence of this clone is presented in Figure 4 and SEQ ID NO:75. Osteonectin, unspliced and unaltered, was also identified from such assays independently.

Further clones identified by this method are referred to herein as 3f, 6b, 8e, 8h, 12c and 12h. Sequences of these clones are shown in Figures 5 to 9 and SEQ ID NO:76 to 81. Microarray analyses were performed as described above, and are presented in Figures 10 to 14. A full length sequence encompassing clones 3f, 6b, 8e

and 12h was obtained by screening an ovarian tumor (SCID-derived) cDNA library. This 2996 base pair sequence (designated O772P) is presented in SEQ ID NO:311, and the encoded 914 amino acid protein sequence is shown in SEQ ID NO:312. PSORT analysis indicates a Type 1a transmembrane protein localized to the plasma membrane.

In addition to certain of the sequences described above, this screen identified the following sequences which are described in detail in Table 1:

Table 1

Sequence	Comments
OV4vG11 (SEQ ID NO:313)	human clone 1119D9 on chromosome 20p12
OV4vB11 (SEQ ID NO:314)	human UWGC:y14c094 from chromosome 6p21
OV4vD9 (SEQ ID NO:315)	human clone 1049G16 chromosome 20q12-13.2
OV4vD5 (SEQ ID NO:316)	human KIAA0014 gene
OV4vC2 (SEQ ID NO:317)	human KIAA0084 gene
OV4vF3 (SEQ ID NO:318)	human chromosome 19 cosmid R31167
OV4VC1 (SEQ ID NO:319)	novel
OV4vH3 (SEQ ID NO:320)	novel
OV4vD2 (SEQ ID NO:321)	novel
O815P (SEQ ID NO:322)	novel
OV4vC12 (SEQ ID NO:323)	novel
OV4vA4 (SEQ ID NO:324)	novel
OV4vA3 (SEQ ID NO:325)	novel
OV4v2A5 (SEQ ID NO:326)	novel
O819P (SEQ ID NO:327)	novel
O818P (SEQ ID NO:328)	novel
O817P (SEQ ID NO:329)	novel
O816P (SEQ ID NO:330)	novel .
Ov4vC5 (SEQ ID NO:331)	novel
21721 (SEQ ID NO:332)	human lumican
21719 (SEQ ID NO:333)	human retinoic acid-binding protein II
21717 (SEQ ID NO:334)	human26S proteasome ATPase subunit
21654 (SEQ ID NO:335)	human copine I
21627 (SEQ ID NO:336)	human neuron specific gamma-2 enolase

61

Sequence	Comments	
21623 (SEQ ID NO:337)	human geranylgeranyl transferase II	
21621 (SEQ ID NO:338)	human cyclin-dependent protein kinase	
21616 (SEQ ID NO:339)	human prepro-megakaryocyte potentiating factor	
21612 (SEQ ID NO:340)	human UPH1	
21558 (SEQ ID NO:341)	human RalGDS-like 2 (RGL2)	
21555 (SEQ ID NO:342)	human autoantigen P542	
21548 (SEQ ID NO:343)	human actin-related protein (ARP2)	
21462 (SEQ ID NO:344)	human huntingtin interacting protein	
21441 (SEQ ID NO:345)	human 90K product (tumor associated antigen)	
21439 (SEQ ID NO:346)	human guanine nucleotide regulator protein (tim1)	
21438 (SEQ ID NO:347)	human Ku autoimmune (p70/p80) antigen	
21237 (SEQ ID NO:348)	human S-laminin	
21436 (SEQ ID NO:349)	human ribophorin I	
21435 (SEQ ID NO:350)	human cytoplasmic chaperonin hTRiC5	
21425 (SEQ ID NO:351)	humanEMX2	
21423 (SEQ ID NO:352)	human p87/p89 gene	
21419 (SEQ ID NO:353)	human HPBRII-7	
21252 (SEQ ID NO:354)	human T1-227H	
21251 (SEQ ID NO:355)	human cullin I	
21247 (SEQ ID NO:356)	kunitz type protease inhibitor (KOP)	
21244-1 (SEQ ID NO:357)	human protein tyrosine phosphatase receptor F (PTPRF)	
21718 (SEQ ID NO:358)	human LTR repeat	
OV2-90 (SEQ ID NO:359)	novel	
Human zinc finger (SEQ ID NO:360)		
Human polyA binding protein (SEQ ID NO:361)		
Human pleitrophin (SEQ ID NO:362)		
Human PAC clone 278C19 (SEQ ID NO:363)		
Human LLRep3 (SEQ ID NO:364)		
Human Kunitz type protease inhib (SEQ ID NO:365)		
Human KIAA0106 gene (SEQ ID NO:366)		
Human keratin (SEQ ID NO:367)		
Human HIV-1TAR (SEQ ID NO:368)		
Human glia derived nexin (SEQ ID NO:369)		

Sequence	Comments	
Human fibronectin (SEQ ID NO:370)		
Human ECMproBM40 (SEQ ID NO:371)		
Human collagen (SEQ ID NO:372)		
Human alpha enolase (SEQ ID NO:373)		
Human aldolase (SEQ ID NO:374)		
Human transf growth factor BIG H3 (SEQ ID NO:375)		
Human SPARC osteonectin (SEQ ID NO:376)		
Human SLP1 leucocyte protease (SEQ ID NO:377)		
Human mitochondrial ATP synth (SEQ ID NO:378)		
Human DNA seq clone 461P17 (SEQ ID NO:379)		
Human dbpB pro Y box (SEQ ID NO:380)		
Human 40 kDa keratin (SEQ ID NO:381)		
Human arginosuccinate synth (SEQ ID NO:382)		
Human acidic ribosomal phosphoprotein (SEQ ID NO:383)		
Human colon carcinoma laminin binding pro (SEQ ID NO:384)		

This screen further identified multiple forms of the clone O772P, referred to herein as 21013, 21003 and 21008. PSORT analysis indicates that 21003 (SEQ ID NO:386; translated as SEQ ID NO:389) and 21008 (SEQ ID NO:387; translated as SEQ ID NO:390) represent Type 1a transmembrane protein forms of O772P. 21013 (SEQ ID NO:385; translated as SEQ ID NO:388) appears to be a truncated form of the protein and is predicted by PSORT analysis to be a secreted protein.

Additional sequence analysis resulted in a full length clone for O8E (2627 bp, which agrees with the message size observed by Northern analysis; SEQ ID NO:391). This nucleotide sequence was obtained as follows: the original O8E sequence (OrigO8Econs) was found to overlap by 33 nucleotides with a sequence from an EST clone (IMAGE#1987589). This clone provided 1042 additional nucleotides upstream of the original O8E sequence. The link between the EST and O8E was confirmed by sequencing multiple PCR fragments generated from an ovary primary tumor library using primers to the unique EST and the O8E sequence (ESTxO8EPCR). Full length status was further indicated when anchored PCR from the ovary tumor library gave

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several clones (AnchoredPCR cons) that all terminated upstream of the putative start methionine, but failed to yield any additional sequence information. Figure 16 presents a diagram that illustrates the location of each partial sequence within the full length O8E sequence.

Two protein sequences may be translated from the full length O8E. For "a" (SEQ ID NO:393) begins with a putative start methionine. A second form "b" (SEQ ID NO:392) includes 27 additional upstream residues to the 5' end of the nucleotide sequence.

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EXAMPLE 3

This example discloses the identification and characterization of antibody epitopes recognized by the O8E polyclonal anti-sera.

Rabbit anti-sera was raised against E. coli derived O8E recombinant protein and tested for antibody epitope recognition against 20 or 21 mer peptides that correspond to the O8E amino acid sequence. Peptides spanning amino acid regions 31 to 65, 76 to 110, 136 to 200 and 226 to 245 of the full length O8E protein were recognized by an acid eluted peak and/or a salt eluted peak from affinity purified anti-O8E sera. Thus, the corresponding amino acid sequences of the above peptides constitute the antibody epitopes recognized by affinity purified anti-O8E antibodies.

ELISA analysis of anti-08E rabbit sera is shown in Figure 23, and ELISA analysis of affinity purified rabbit anti-08E polyclonal antibody is shown in Figure 24.

For epitope mapping, 20 or 21 mer peptides corresponding to the O8E protein were synthesized. For antibody affinity purification, rabbit anti-O8E sera was run over an O8E-sepharose column, then antibody was eluted with a salt buffer containing 0.5 M NaCl and 20 mM PO₄, followed by an acid elution step using 0.2 M Glycine, pH 2.3. Purified antibody was neutralized by the addition of 1M Tris, pH 8 and buffer exchanged into phosphate buffered saline (PBS). For enzyme linked immunosorbant assay (ELISA) analysis, O8E peptides and O8E recombinant protein were coated onto 96 well flat bottom plates at 2 μg/ml for 2 hours at room temperature (RT). Plates were then washed 5 times with PBS + 0.1 % Tween 20 and blocked with PBS + 1 % bovine serum albumin (BSA) for 1 hour. Affinity purified anti-O8E antibody, either an acid or salt eluted fraction, was then added to the wells at 1 μg/ml

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and incubated at RT for 1 hr. Plates were again washed, followed by the addition of donkey anti-rabbit-Ig-horseradish peroxidase (HRP) antibody for 1 hour at RT. Plates were washed, then developed by the addition of the chromagenic substrate 3, 3', 5, 5'-tetramethylbenzidine (TMB) (described by Bos et al., J. of Immunoassay 2:187-204 (1981); available from Sigma (St. Louis, MO)). The reaction was incubated 15 minutes at RT and then stopped by the addition of 1 N H₂SO₄. Plates were read at an optical density of 450 (OD450) in an automated plate reader. The sequences of peptides corresponding to the OE8 antibody epitopes are disclosed herein as SEQ ID NO: 394-415. Antibody epitopes recognized by the O8E polyclonal anti-sera are disclosed herein in Figure 17.

EXAMPLE 4

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This example discloses IHC analysis of O8E expression in ovarian cancer tissue samples.

For immunohistochemistry studies, paraffin-embedded formalin fixed ovarian cancer tissue was sliced into 8 micron sections. Steam heat induced epitope retrieval (SHIER) in 0.1 M sodium citrate buffer (pH 6.0) was used for optimal staining conditions. Sections were incubated with 10% serum/PBS for 5 minutes. Primary antibody (anti-O8E rabbit affinity purified polyclonal antibody) was added to each section for 25 min followed by a 25 min incubation with an anti-rabbit biotinylated antibody. Endogenous peroxidase activity was blocked by three 1.5 min incubations with hydrogen peroxidase. The avidin biotin complex/horse radish peroxidase system was used along with DAB chromogen to visualize antigen expression. Slides were counterstained with hematoxylin. One (papillary serous carcinoma) of six ovarian cancer tissue sections displayed O8E immunoreactivity. Upon optimization of the staining conditions, 4/5 ovarian cancer samples stained positive using the O8E polyclonal antibody. O8E expression was localized to the plasma membrane.

Six ovarian cancer tissues were analyzed with the anti-O8E rabbit polyclonal antibody. One (papillary serous carcinoma) of six ovarian cancer tissue samples stained positive for O8E expression. O8E expression was localized to the surface membrane.

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WO 02/06317 PCT/US01/22635

EXAMPLE 5

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This example discloses O8E peptides that are predicted to bind HLA-A2 and to be immunogenic for CD8 T cell responses in humans.

Potential HLA-A2 binding peptides of O8E were predicted by using the full-length open-reading frame (ORF) from O8E and running it through "Episeek," a program used to predict MHC binding peptides. The program used is based on the algorithm published by Parker, K.C. et al., J. Immunol. 152(1):163-175 (1994) (incorporated by reference herein in its entirety). 10-mer and 9-mer peptides predicted to bind HLA-0201 are disclosed herein as SEQ ID NO: 416-435 and SEQ ID NO: 436-455, respectively.

EXAMPLE 6

This example discloses O8E cell surface expression measured by fluoresence activated cell sorting.

For FACS analysis, cells were washed with ice cold staining buffer (PBS/1% BSA/azide). Next, the cells were incubated for 30 minutes on ice with 10 micrograms/ml of affinity purified rabbit anti-B305D polyclonal antibody. The cells were washed 3 times with staining buffer and then incubated with a 1:100 dilution of a goat anti-rabbit Ig (H+L)-FITC reagent (Southern Biotechnology) for 30 minutes on ice. Following 3 washes, the cells were resuspended in staining buffer containing prodium iodide, a vital stain that allows for identification of permeable cells, and analyzed by FACS. O8E surface expression was confirmed on SKBR3 breast cancer cells and HEK293 cells that stably overexpress the cDNA for O8E. Neither MB415 cells nor HEK293 cells stably transfected with a control irrelevant plasmid DNA showed surface expression of O8E (Figures 18 and 19).

25 EXAMPLE 7

This example further evaluates the expression and surface localization of O8E.

For expression and purification of antigen used for immunization, O8E expressed in an E. coli recombinant expression system was grown overnight in LB Broth with the appropriate antibiotics at 37°C in a shaking incubator. The next morning,

10 ml of the overnight culture was added to 500 ml of 2x YT plus appropriate antibiotics in a 2L-baffled Erlenmeyer flask. When the Optical Density (at 560 nanometers) of the culture reached 0.4-0.6 the cells were induced with IPTG (1 mM). 4 hours after induction with IPTG the cells were harvested by centrifugation. The cells were then washed with phosphate buffered saline and centrifuged again. The supernatant was discarded and the cells were either frozen for future use or immediately processed. Twenty milliliters of lysis buffer was added to the cell pellets and vortexed. To break open the E. coli cells, this mixture was then run through the French Press at a pressure of 16,000 psi. The cells were then centrifuged again and the supernatant and pellet were checked by SDS-PAGE for the partitioning of the recombinant protein. For protein that localized to the cell pellet, the pellet was resuspended in 10 mM Tris pH 8.0 , 1% CHAPS and the inclusion body pellet was washed and centrifuged again. This procedure was repeated twice more. The washed inclusion body pellet was solubilized with either 8 M urea or 6 M guanidine HCl containing 10 mM Tris pH 8.0 plus 10 mM imidazole. The solubilized protein was added to 5 ml of nickel-chelate resin (Qiagen) and incubated for 45 min to 1 hour at room temperature with continuous agitation. After incubation, the resin and protein mixture were poured through a disposable column and the flow through was collected. The column was then washed with 10-20 column volumes of the solubilization buffer. The antigen was then eluted from the column using 8M urea, 10 mM tris pH 8.0 and 300 mM imidazole and collected in 3 ml fractions. A SDS-PAGE gel was run to determine which fractions to pool for further purification. As a final purification step, a strong anion exchange resin such as Hi-Prep Q (Biorad) was equilibrated with the appropriate buffer and the pooled fractions from above were loaded onto the column. Each antigen was eluted off of the column with an increasing salt gradient. Fractions were collected as the column was run and another SDS-PAGE gel was run to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10 mM Tris pH 8.0. This material was then evaluated for acceptable purity as determined by SDS-PAGE or HPLC, concentration as determined by Lowry assay or Amino Acid Analysis, identity as determined by amino terminal protein sequence, and endotoxin level as determined by the Limulus (LAL) assay. The

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WO 02/06317 PCT/US01/22635

proteins were then vialed after filtration through a 0.22 micron filter and the antigens were frozen until needed for immunization.

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For generation of polyclonal anti-sera, 400 micrograms of each prostate antigen was combined with 100 micrograms of muramyldipeptide (MDP). Equal volume of Incomplete Freund's Adjuvant (IFA) was added and then mixed. Every four weeks animals were boosted with 100 micrograms of antigen mixed with an equal volume of IFA. Seven days following each boost the animal was bled. Sera was generated by incubating the blood at 4°C for 12-24 hours followed by centrifugation.

For characterization of polyclonal antisera, 96 well plates were coated with antigen by incubating with 50 microliters (typically 1 microgram) at 4°C for 20 hrs. 250 microliters of BSA blocking buffer was added to the wells and incubated at RT for 2 hrs. Plates were washed 6 times with PBS/0.01% tween. Anti-O8E rabbit sera or affinity purified anti-O8e antibody was diluted in PBS. Fifty microliters of diluted antibody was added to each well and incubated at RT for 30 min. Plates were washed as described above before 50 microliters of goat anti-rabbit horse radish peroxidase (HRP) at a 1:10000 dilution was added and incubated at RT for 30 min. Plates were washed as described above and 100 microliters of TMB microwell Peroxidase Substrate was added to each well. Following a 15 minute incubation in the dark at room temperature the colorimetric reaction was stopped with 100 microliters of 1N H2SO4 and read immediately at 450 nm. All polyclonal antibodies showed immunoreactivity to the O8E antigen.

For recombinant expression in mammalian HEK293 cells, full length O8E cDNA was subcloned into the mammalian expression vectors pcDNA3.1+ and pCEP4 (Invitrogen) which were modified to contain His and FLAG epitope tags, respectively. These constructs were transfected into HEK293 cells (ATCC) using Fugene 6 reagent (Roche). Briefly, HEK293 cells were plated at a density of 100,000 cells/ml in DMEM (Gibco) containing 10% FBS (Hyclone) and grown overnight. The following day, 2 ul of Fugene6 was added to 100 ul of DMEM containing no FBS and incubated for 15 minutes at room temperature. The Fugene6/DMEM mixture was then added to lug of O8E/pCEP4 or O8E/pcDNA3.1 plasmid DNA and incubated for 15 minutes at room temperature. The Fugene/DNA mix was then added to the HEK293

cells and incubated for 48-72 hrs at 37oC with 7% CO2. Cells were rinsed with PBS then collected and pelleted by centrifugation. For Western blot analysis, whole cell lysates were generated by incubating the cells in Triton-X100 containing lysis buffer for 30 minutes on ice. Lysates were then cleared by centrifugation at 10,000rpm for 5 minutes at 4 C. Samples were diluted with SDS-PAGE loading buffer containing beta-mercaptoethanol, then boiled for 10 minutes prior to loading the SDS-PAGE gel. Protein was transferred to nitrocellulose and probed using anti-O8E rabbit polyclonal sera #2333L at a dilution of 1:750. The blot was revealed with a goat anti-rabbit Ig coupled to HRP followed by incubation in ECL substrate.

For FACS analysis, cells were washed further with ice cold staining buffer (PBS+1%BSA+Azide). Next, the cells were incubated for 30 minutes on ice with 10ug/ml of Protein A purified anti-O8E polyclonal sera. The cells were washed 3 times with staining buffer and then incubated with a 1:100 dilution of a goat anti-rabbit Ig(H+L)-FITC reagent (Southern Biotechnology) for 30 minutes on ice. Following 3 washes, the cells were resuspended in staining buffer containing Propidium Iodide (PI), a vital stain that allows for the identification of permeable cells, and analyzed by FACS.

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From these experiments, the results of which are illustrated in Figures 20-21, O8E expression was detected on the surface of transfected HEK293 cells and SKBR3 cells by FACS analysis using rabbit anti-O8E sera. Expression was also detected in transfected HEK293 cell lysates by Western blot analysis (Figure 22).

EXAMPLE 8

GENERATION AND CHARACTERIZATION OF ANTI-O8E MABS.

Mouse monoclonal antibodies were raised against E. coli derived O8E proteins as follows. A/J mice were immunized intraperitoneally (IP) with Complete Freund's Adjuvant (CFA) containing 50 µg recombinant O8E, followed by a subsequent IP boost with Incomplete Freund's Adjuvant (IFA) containing 10µg recombinant O8E protein. Three days prior to removal of the spleens, the mice were immunized intravenously with approximately 50µg of soluble O8E recombinant protein. The spleen of a mouse with a positive titer to O8E was removed, and a single-cell suspension made and used for fusion to SP2/0 myeloma cells to generate B cell

WO 02/06317

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hybridomas. The supernatants from the hybrid clones were tested by ELISA for specificity to recombinant O8E, and epitope mapped using peptides that spanned the entire O8E sequence. The mAbs were also tested by flow cytometry for their ability to detect O8E on the surface of cells stably transfected with O8E and on the surface of a breast tumor cell line.

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For ELISA analysis, 96 well plates were coated with either recombinant O8E protein or overlapping 20-mer peptides spanning the entire O8E molecule at a concentration of either 1-2µg/ml or 10µg/ml, respectively. After coating, the plates were washed 5 times with washing buffer (PBS + 0.1% Tween-20) and blocked with PBS containing 0.5% BSA, 0.4% Tween-20. Hybrid supernatants or purified mAbs were then added and the plates incubated for 60 minutes at room temperature. The plates were washed 5 times with washing buffer and the secondary antibody, donkeyanti mouse Ig linked to horseradish peroxidase (HRP)(Jackson ImmunoResearch), was added for 60 minutes. The plates were again washed 5 times in washing buffer, followed by the addition of the peroxidase substrate. Of the hybridoma clones generated, 15 secreted mAbs that recognized the entire O8E protein. Epitope mapping revealed that of these 15 clones, 14 secreted mAbs that recognized the O8E amino acid residues 61-80 and one clone secreted a mAb that recognized amino acid residues 151-170.

For flow cytometric analysis, HEK293 cells which had been stably transfected with O8E and SKBR3 cells which express O8E mRNA, were harvested and washed in flow staining buffer (PBS+1%BSA+Azide). The cells were incubated with the supernatant from the mAb hybrids for 30 minutes on ice followed by 3 washes with staining buffer. The cells were incubated with goat-anti mouse Ig-FITC for 30 minutes on ice, followed by three washes with staining buffer before being resuspended in wash buffer containing propidium iodide. Flow cytometric analysis revealed that 15/15 mAbs were able to detect O8E protein expressed on the surface of O8E-transfected HEK293 cells. 6/6 mAbs tested on SKBR3 cells were able to recognize surface expressed O8E.

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EXAMPLE 9

EXTENDED DNA AND PROTEIN SEQUENCE ANALYSIS OF SEQUENCE O772P

A full-length sequence encompassing clones 3f, 6b, 8e, and 12 was obtained by screening an ovarian tumor (SCID-derived) cDNA library described in detail in Example 2. This 2996 base pair sequence, designated O772P, is presented in SEQ ID NO: 311, and the encoded 914 amino acid protein sequence is shown in SEQ ID NO: 312. The DNA sequence O772P was searched against public databases including Genbank and showed a significant hit to Genbank Accession number AK024365 (SEQ ID NO: 457). This Genbank sequence was found to be 3557 base pairs in length and encodes a protein 1156 amino acids in length (SEQ ID NO: 459). A truncated version of this sequence, residues 25-3471, in which residue 25 corresponds to the first ATG initiation codon in the Genbank sequence, (SEQ ID NO: 456), encodes a protein that is 1148 amino acids in length (SEQ ID NO: 458). The published DNA sequence (SEQ ID NO: 457) differs from O772P in that it has a 5 base pair insertion corresponding to bases 958-962 of SEQ ID NO: 457. This insertion results in a frame shift such that SEQ ID NO: 457 encodes an additional N-terminal protein sequence relative to O772P (SEQ ID NO: 312). In addition, O772P encodes a unique N-terminal portion contained in residues 1-79 (SEQ ID NO: 460). The N-terminal portion of SEQ ID NO: 456, residues 1-313, also contains unique sequence and is listed as SEQ ID NO: 461.

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EXAMPLE 10

THE GENERATION OF POLYCLONAL ANTIBODIES FOR IMMUNOHISTOCHEMISTRY

AND FLOW CYTOMETRIC ANALYSIS OF THE CELL ASSOCIATED EXPRESSION

PATTERN OF MOLECULE O772P

The O772P molecule was identified in Examples 2 and 9 of this application. To evaluate the subcellular localization and specificity of antigen expression in various tissues, polyclonal antibodies were generated against O772P. To produce these antibodies, O772P-1 (amino acids 44-772 of SEQ ID NO:312) and O772P-2 (477-914 of SEQ ID NO:312) were expressed in an E. coli recombinant expression system and grown overnight at 37°C in LB Broth. The following day, 10ml

WO 02/06317

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PCT/US01/22635

of the overnight culture was added to 500ml of 2xYT containing the appropriate antibiotics. When the optical density of the cultures (560 nanometers) reached 0.4-0.6 the cells were induced with IPTG. Following induction, the cells were harvested, washed, lysed and run through a French Press at a pressure of 16000 psi. The cells were then centrifuged and the pellet checked by SDS-PAGE for the partitioning of the recombinant protein. For proteins that localize to the cell pellet, the pellet was resuspended in 10mM Tris, pH 8.0, 1% CHAPS and the inclusion body pellet washed and centrifuged. The washed inclusion body was solubilized with either 8M urea or 6M guanidine HCL containing 10mM Tris, pH 8.0, plus 10mM imidazole. The solubilized protein was then added to 5ml of nickel-chelate resin (Qiagen) and incubated for 45 minutes at room temperature.

Following the incubation, the resin and protein mixture was poured through a column and the flow through collected. The column was washed with 10-20 column volumes of buffer and the antigen eluted using 8M urea, 10mM Tris, pH 8.0, and 300 mM imidazole and collected in 3ml fractions. SDS-PAGE was run to determine which fractions to pool for further purification. As a final purification step, a strong anion exchange resin was equilibrated with the appropriate buffer and the pooled fractions were loaded onto the column. Each antigen was eluted from the column with an increasing salt gradient. Fractions were collected and analyzed by a SDS-PAGE to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10mM Tris, pH 8.0, and the resulting protein was submitted for quality control for final release. The release criteria were: (a) purity as determined by SDS-PAGE or HPLC, (b) concentration as determined by Lowry assay or Amino Acid Analysis, (c) identity as determined by amino terminal protein, and (d) endotoxin levels as determined by the Limulus (LAL) assay. The proteins were then filtered through a 0.22µM filter and frozen until needed for immunizations.

To generate polyclonal antisera, 400µg of O772P-1 or O772P-2 was combined with 100µg of muramyldipeptide (MDP). The rabbits were immunized every 4 weeks with 100µg of antigen mixed with an equal volume of Incomplete Freund's Adjuvant (IFA). Seven days following each boost, the animals were bled and sera was generated by incubating the blood at 4°C for 12-24 hours followed by centrifugation.

PCT/US01/22635

To characterize the antisera, 96 well plates were coated with antigen followed by blocking with BSA. Rabbit sera was diluted in PBS and added to each well. The plates were then washed, and goat anti-rabbit horseradish peroxidase (HRP). The plates were again washed and TMB microwell Peroxidase Substrate was added. Following this incubation, the colormetric reaction was stopped and the plates read immediately at 450nm. All polyclonal antibodies showed immunoreactivity to the appropriate antigen.

Immunohistochemistry analysis of O772P expression was performed on paraffin-embedded formalin fixed tissue. O772P was found to be expressed in normal ovary and ovarian tumor, but not in normal heart, kidney, colon, lung or liver. Additionally, immunohistochemistry and flow cytometric analysis indicates that O772P is a plasma membrane-associated molecule. O772P contains 1 plasma transmembrane domain predicted to be encoded by amino acids 859-880. The N-terminus of O772P is extracellular and is encoded by amino acids 1-859, while the C-terminus is intracellular. Sequence analysis shows that there are 17 potential N-linked glycosylation sites.

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EXAMPLE 11

O772P IS EXPRESSED ON THE SURFACE OF PRIMARY OVARIAN TUMOR CELLS

For recombinant expression in mammalian cells, the O772P-21008 (SEQ ID NO:387) and O772P full length cDNA (SEQ ID NO:311 encoding the protein of SEQ ID NO:312) were subcloned into mammalian expression vectors pBIB or pCEP4 respectively. These constructs were transfected into HEK293 cells using Fugene 6 (Roche). The HEK cells were then plated at a density of 100,000 cells/ml in DMEM containing fetal bovine serum (FBS) and grown overnight. The following day, 2µl of Fugene 6 was added to 100µl of DMEM, which contained no FBS, and incubated for 15 minutes at room temperature. The Fugene 6/DMEM mixture was then added to 1 µg of O772P/pBIB or O772P/pCEP4 plasmid DNA and incubated for an additional 15 minutes at room temperature. The Fugene 6/DNA mix was then added to the HEK293 cells and incubated for 48-72 hours at 37°C with 7% CO2. The cells were rinsed and pelleted by centrifugation.

WO 02/06317

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For Western Blot analysis, whole cell lysates were generated by incubating the cells in lysis buffer followed by clarification by centrifugation. The samples were diluted and run on SDS-PAGE. The gel was then transferred to nitrocellulose and probed using purified anti-O772P-2 rabbit polyclonal antibody. The blot was revealed with a goat anti-rabbit Ig coupled to HRP followed by incubation in ECL substrate. Western Blot analysis revealed that O772P-21008 could be detected in HEK293 cells that had been transfected with O772P.

To determine the cell expression profile of O772P in cells, primary ovarian tumor cells were grown in SCID mice. The cells were retrieved from the mice and analyzed by flow cytometry. Briefly, cells washed in cold staining buffer containing PBS, 1% BSA, and Na Azide. The cells were incubated for 30 minutes with 10µg/ml of purified anti-O772P-1 and O772P-2 polyclonal sera. Following this incubation, the cells were washed three times in staining buffer and incubated with goat anti-rabbit Ig (H+L) conjugated to FITC (Southern Biotechnology). The cells were washed and resuspended in staining buffer containing Propidium Iodide (PI), a vital stain that identifies non-viable cells. The cells were then analyzed using Fluorescence Activated Cell Sorting (FACS). FACS analysis revealed that O772P was present on the cells surface. Surface expression of O772P on tumor cells allows for immune targeting by therapeutic antibodies.

20 EXAMPLE 12

FUNCTIONAL CHARACTERIZATION OF ANTI-O8E MONOCLONAL ANTIBODIES

Mouse monoclonal antibodies (mAb) raised against E. coli derived O8E, as described in Example 8, were tested for their ability to promote O8E antigen internalization. Internalization of the antibody was determined using an in vitro cytotoxicity assay. Briefly, HEK293 and O8E/HEK transfected cells were plated into 96 well plates containing DME plus 10% heat-inactivated FBS in the presence of 50ng/well of purified anti-O8E or control antibodies. The isotype of the anti-O8E mAbs are as follows: 11A6-IgG1/kappa, 15C6-IgG2b/kappa, 18A8-IgG2b/kappa, and 14F1-IgG2a/kappa. W6/32 is a pan anti-human MHC class I mouse monoclonal antibody that serves as a positive control, and two irrelevant mAbs, Ir-Pharm and Ir-

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WO 02/06317 PCT/US01/22635

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Crxa were included as negative controls. Following incubation with the O8E specific antibodies or the relevant controls antibodies, the mAb-zap, a goat anti-mouse Igsaporin conjugated secondary antibody (Advanced Targeting Systems) was added at a concentration of 100ng/ml to half of the wells, and the plates were incubated for 48 to 72 hours at 37°C in a 7% CO₂ incubator. This assay takes advantage of the toxic nature of saporin, a ribozyme inactivating protein, which when internalized has a cytotoxic effect. Following incubation with the mAb-zap, internalization was quantitated by the addition of MTS reagent, followed by reading the OD490 of the plate on a microplate ELISA reader. Figure 25 depicts the results from these assays. The top panel represents HEK cells that have not been transfected with O8E and therefore O8E antibody should not bind and be internalized. Levels of proliferation were the same in all samples whether they were incubated with or without the mAb-zap, with the exception of the positive control Ab, W6/32. The lower panel represents cells that have been transfected with O8E and therefore should bind O8E specific antibodies. Antibodies from the hybridomas 11H6, 14F1, and 15C6, which recognize the amino acids 61-80 of O8E were able to promote internalization of the O8E surface protein as measured by decreased levels of proliferation due to the toxic nature of the mAb-zap (See Figure 25). The antibody generated by the hybridoma 18A8, which recognizes amino acids 151-170 of O8E, was unable to promote internalization as determined by normal levels of proliferation either in the absence or presence of the mAb-zap.

EXAMPLE 13

CHARACTERIZATION OF THE OVARIAN TUMOR ANTIGEN, O772P

The cDNA and protein sequences for multiple forms of the ovarian tumor antigen O772P have been described in the above (e.g., Examples 2 and 9). A Genbank search indicated that O772P has a high degree of similarity with FLJ14303 (Accession # AK024365; SEQ ID NO:457 and 463). Protein sequences corresponding to O772P and FLJ14303 are disclosed in SEQ ID NO:478 and 479, respectively. FLJ14303 was identical to the majority of O772P, with much of the 3'-end showing 100% homology. However, the 5'-end of FLJ14303 was found to extend further 5' than O772P. In addition, FLJ14303 contained a 5 bp insert (SEQ ID NO:457) resulting in a

frame shift of the amino-terminus protein sequence such that FLJ14303 utilizes a different starting methionine than O772P and therefore encodes a different protein. This insertion was present in the genomic sequence and seen in all EST clones that showed identity to this region, suggesting that FLJ14303 (SEQ ID NO:457) represents a splice variant of O772P, with an ORF that contains an extended and different amino-terminus. The additional 5'-nucleotide sequence included repeat sequences that were identified during the genomic mapping of O772P. The 5'-end of O772P and the corresponding region of FLJ14303 showed between 90-100% homology. Taken together, this suggests that O772P and FLJ14303 are different splice variants of the same gene, with different unique repeat sequences being spliced into the 5'-end of the gene.

The identification of an additional ten or more repeat sequences within the same region of chromosome 19, indicates that there may be many forms of O772P, each with a different 5'-end, due to differential splicing of different repeat sequences. Northern blot analysis of O772P demonstrated multiple O772P-hybridizing transcripts of different sizes, some in excess 10kb.

Upon further analysis, 13 additional O772P-related sequences were identified, the cDNA and amino acid sequences of which are described in Table 2.

Table 2

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SEQ ID NO:	Description	Transmembrane Domains
464	LS #1043400.1 (cDNA)	nd
465	LS #1043400.10 (cDNA)	0
466	LS #1043400.11 (cDNA)	2
467	LS #1043400.12 (cDNA)	2
468	LS #1043400.2 (cDNA)	nd
469	LS #1043400.3 (cDNA)	
470	LS #1043400.5 (cDNA)	nd
471	LS #1043400.8 (cDNA)	1
472	LS #1043400.9 (cDNA)	0

LS #1043400.6 (cDNA)	nd
LS #1043400.7 (cDNA)	nd
LS #1043400.4 (cDNA)	nd
LS #1397610.1 (cDNA)	0
1043400.10 Novel 5' (cDNA)	-
LS #1043400.9 (amino acid)	-
LS #1043400.8B (amino acid)	-
Contains a transmembrane	
domain	
LS #1043400.8A (amino acid)	
LS #1043400.12 (amino acid)	- ·
Contains a transmembrane	
domain	
LS #1043400.11B (amino acid)	-
Contains a transmembrane	
domain	
LS #1043400.11A (amino acid)	-
LS #1043400.10 (amino acid)	-
LS #1043400.1 (amino acid)	_
	LS #1043400.7 (cDNA) LS #1043400.4 (cDNA) LS #1397610.1 (cDNA) 1043400.10 Novel 5' (cDNA) LS #1043400.9 (amino acid) LS #1043400.8B (amino acid) Contains a transmembrane domain LS #1043400.8A (amino acid) LS #1043400.12 (amino acid) Contains a transmembrane domain LS #1043400.11B (amino acid) Contains a transmembrane domain LS #1043400.11B (amino acid) Contains a transmembrane domain LS #1043400.11A (amino acid) LS #1043400.11A (amino acid)

nd=not determined

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Initially it appeared that these sequences represented overlapping and/or discrete sequences of O772P splice forms that were capable of encoding polypeptides unique to the specific splice forms of O772P. However, nucleotide alignment of these sequences failed to identify any identical regions within the repeat elements. This indicates that the sequences may represent different specific regions of a single O772P gene, one that contains 16 or more repeat domains, all of which form a single linear transcript. The 5'-end of sequence LS #1043400.10 (Table 2; SEQ ID NO:465) is unique to both O772P and FLJ14303 and contains no repeat elements, indicating that this sequence may represent the 5'-end of O772P.

Previously, transmembrane prediction analysis had indicated that O772P contained between 1 and 3 transmembrane spanning domains. This was verified by the

use of immunohistochemistry and flow cytometry, which demonstrated the existence of a plasma membrane-associated molecule representing O772P. However, immunohistochemistry also indicated the presence of secreted form(s) of O772P, possibly resulting from an alternative splice form of O772P or from a post-translational cleavage event. Analysis of several of the sequences presented in Table 2 showed that sequences 1043400B.12, 1043400.8B, and 1043400.11B all contained transmembrane regions, while 1043400.8A, 1043400.10, 1043400.1, 1043400.11A, and 1043400.9 were all lacking transmembrane sequences, suggesting that these proteins may be secreted.

Analysis indicates a part of O772P is expressed and/or retained on the plasma membrane, making O772P an attractive target for directing specific immunotherapies, e.g., therapeutic antibodies, against this protein. The predicted extracellular domain of O772P is disclosed in SEQ ID NO:489 and secretion of O772P is likely to occur as a result of a cleavage event within the sequence:

SLVEQVFLD<u>K</u>TLNASFHWLGSTYQLVDIHVTEMESSVYQP.

Proteolytic cleavage is most likely to occur at the Lysine (K) at position 10 of SEQ ID NO:489. The extracellular, transmembrane, and cytoplasmic regions of O772P are all disclosed in SEQ ID NO:488:

Extracellular:

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SLVEQVFLDKTLNASFHWLGSTYQLVDIHVTEMESSVYQPTSSSS
TQHFYLNFTITNLPYSQDKAQPGTTNYQRNKRNIEDALNQLFRNSSIKSYFSDCQ
VSTFRSVPNRHHTGVDSLCNFSPLARRVDRVAIYEEFLRMTRNGTQLQNFTLDR
SSVLVDGYFPNRNEPLTGNSDLPF

Transmembrane:

WAVILIGLAGLLGLITCLICGVLVTT

Cytoplasmic:

RRRKKEGEYNVQQQCPGYYQSHLDLEDLQ

EXAMPLE 14

IMMUNOHISTOCHEMISTRY (IHC) ANALYSIS OF O8E EXPRESSION IN OVARIAN CANCER AND NORMAL TISSUES

In order to determine which tissues express the ovarian cancer antigen O8E, IHC analysis was performed on a diverse range of tissue sections using both polyclonal and monoclonal antibodies specific for O8E. The generation of O8E specific polyclonal antibodies is described in detail in Example 8. The monoclonal antibodies used for staining were 11A6 and 14F1, both of which are specific for amino acids 61-80 of O8E and 18A8, which recognizes amino acids 151-170 of O8E (see Example 12 for details on generation).

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To perform staining, tissue samples were fixed in formalin solution for 12-24 hours and embedded in paraffin before being sliced into 8 micron sections. Steam heat induced epitope retrieval (SHEIR) in 0.1M sodium citrate buffer (pH 6.0) was used for optimal staining conditions. Sections were incubated with 10% serum/PBS for 5 minutes. Primary antibody was then added to each section for 25 minutes followed by 25 minutes of incubation with either anti-rabbit or anti-mouse biotinylated antibody. Endogenous peroxidase activity was blocked by three 1.5 minute incubations with hydrogen peroxidase. The avidin biotin complex/horse radish peroxidase (ABC/HRP) system was used along with DAB chromogen to visualize the antigen expression. Slides were counterstained with hematoxylin to visualize the cell nuclei.

Results using rabbit affinity purified polyclonal antibody to O8E (a.a. 29-283; for details on the generation of this Ab, see Example 3) are presented in Table 3. Results using the three monoclonal antibodies are presented in Table 4.

<u>Table 3</u>
<u>Immunohistochemistry analysis of O8E using polyclonal antibodies</u>

Tissue	O8E Expression	
Ovarian Cancer	Positive	
Breast Cancer	Positive	

Normal Ovary	Positive
Normal Breast	Positive
Blood Vessel	Positive
Kidney	Negative
Lung	Negative
Colon	Negative
Liver	Negative
Heart	Negative

<u>Table 4</u>
<u>Immunohistochemistry analysis of O8E using monoclonal antibodies</u>

Normal	11A6		18A8		14F1	
Tissue	Endothelia	Epithelial	Endothelial	Epithelial	Endothelial	Epithelial
	1					
Skin	2	2	0	0	1	1
Skin	1	1	0	0	1	1
Breast	0	1	n/a	n/a	1	1
Colon	0	0	0	0	0	0
Jejunum	0	0	0	0	0	0
Colon	0	0	0	0	0	0
Colon	0	0	0	0	0	0
Ovary	0	0	0	0	1	0 .
Colon	0	0	0	0_	0	1
Liver	0	0	0	0	1	2
Skin	0	0	0	0	1	0
Duodenum	0	0	0	0	0	0
and Pancreas)
Appendix	0	0	0	0	0	0
Ileum	0	0	0	0	0	0

0=no staining, 1=light staining, 2=moderate staining, n/a=not available

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EXAMPLE 15 EPITOPE MAPPING OF O772P POLYCLONAL ANTIBODIES

To perform epitope mapping of O772P, peptides were generated, the sequences of which were derived from the sequence of O772P. These peptides were 15 mers that overlapped by 5 amino acids and were generated via chemical synthesis on membrane supports. The peptides were covalently bound to Whatman 50 cellulose support by their C-terminus with the N-terminus unbound. In order to determine epitope specificity, the membranes were wet with 100% ethanol for 1 minute, and then blocked for 16 hours in TBS/Tween/Triton buffer (50mM Tris, 137 mM NaCl, 2.7 mM 10 KCl, 0.5% BSA, 0.05% Tween 20, 0.05% Triton X-100, pH 7.5). The peptides were then probed with 2 O772P specific antibodies, O772P-1 (amino acids 44-772 of SEQ ID NO:312) and O772P-2 (477-914 of SEQ ID NO:312; see Example 10 for details of antibody generation), as well as irrelevant rabbit antibodies for controls. The antibodies were diluted to lug/ml and incubated with the membranes for 2 hours at room 15 temperature. The membranes were then washed for 30 minutes in TBS/Tween/Triton buffer, prior to being incubated with a 1:10,000 dilution of HRP-conjugated anti-rabbit secondary antibody for 2 hours. The membranes were again washed for 30 minutes in TBS/Tween/Triton and anti-peptide reactivity was visualized using ECL. Specific epitope binding specificity for each of the O772P-polyclonal antibodies is described in Table 5. 20

Table 5

SEQ ID NO:	Peptide #	Anti-O772P1	Anti-O772P2	Peptide Sequence
490	2	***	-	TCGMRRTCSTLAPGS
491	6	*	*/-	CRLTLLRPEKDGTAT
492	7	*	-	DGTATGVDAICTHHP
493	8	-	-	CTHHPDPKSPRLDRE
494	9	***	***	RLDREQLYWELSQLT
495	11	*/-	-	LGPYALDNDSLFVNG
496	13	****	-	SVSTTSTPGTPTYVL
497	22	-	-	LRPEKDGEATGVDAI
498	24	**	*/-	DPTGPGLDREQLYLE
499	27	*/-		LDRDSLYVNGFTHRS
500	40	*/-	-	GPYSLDKDSLYLNGY
501	41	-	-	YLNGYNEPGPDEPPT
502	47	***	***	ATFNSTEGVLQHLLR

503	50	-	***	QLISLRPEKDGAATG
504	51	-	**	GAATGVDTTCTYHPD
505	52	Ţ <u></u>	*/-	TYHPDPVGPGLDIQQ
506	53	-	*	LDIQQLYWELSQLTH
507	58	-	*	HIVNWNLSNPDPTSS
508	59	-	*	DPTSSEYITLLRDIQ
509	60	-	*	LRDIQDKVTTLYKGS
510	61	-	***	LYKGSQLHDTFRFCL
511	71	-	**	DKAQPGTTNYQRNKR

^{*=} relative reactive level, -; no binding, ****; maximal binding

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 ${\bf EXAMPLE~16}$ ${\bf IDENTIFICATION~OF~a~Novel~N-Terminal~Repeat~Structure~Associated~With}$ ${\bf O772P}$

Various O772P cDNA and protein forms have been identified and characterized as detailed above (e.g., Examples 1, 2, 9, and 14). Importantly, O772P RNA and protein have been demonstrated to be over-expressed in ovarian cancer tissue relative to normal tissues and thus represents an attractive target for ovarian cancer diagnostic and therapeutic applications.

Using bioinformatic analysis of open reading frames (ORFs) from genomic nucleotide sequence identified previously as having homology with O772P, multiple nucleotide repeat sequences were identified in the 5' region of the gene encoding the O772P protein. A number of these repeat sequences were confirmed by RT-PCR using primers specific for the individual repeats. Fragments which contained multiple repeats were amplified from cDNA, thus confirming the presence of specific repeats and allowing an order of these repeats to be established.

Unexpectedly, when various sets of O772P sequences derived from different database and laboratory sources were analyzed, at least 20 different repeat structures, each having substantial levels of identity with each other (see Table 6), were identified in the 5' region of the O772P gene and the corresponding N-terminal region of the O772P protein. Each repeat comprises a contiguous open reading frame encoding a polypeptide unit that is capable of being spliced to one or more other repeats such that concatomers of the repeats are formed in differing numbers and orders. Interestingly, other molecules have been described in the scientific literature that have repeating structural domains analogous to those described herein for O772P. For example, the

mucin family of proteins, which are the major glycoprotein component of the mucous which coats the surfaces of cells lining the respiratory, digestive and urogenital tracts, have been shown to be composed of tandemly repeated sequences that vary in number, length and amino acid sequence from one mucin to another (Perez-Vilar and Hill, *J. Biol. Chem. 274(45)*:31751-31754, 1999).

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The various identified repeat structures set forth herein are expected to give rise to multiple forms of O772P, most likely by alternative splicing. The cDNA sequences of the identified repeats are set forth in SEQ ID NOs:513-540, 542-546, and 548-567. The encoded amino acid sequences of the repeats are set forth in SEQ ID NOs:574-593. In many instances these amino acid sequences represent consensus sequences that were derived from the alignment of more than one experimentally derived sequence.

Each of these splice forms is capable of encoding a unique O772P protein with multiple repeat domains attached to a constant carboxy terminal protein portion of O772P that contains a trans membrane region. The cDNA sequence of the O772P constant region is set forth in SEQ ID NO:568 and the encoded amino acid sequence is set forth in SEQ ID NO:594.

All of the available O772P sequences that were obtained were broken down into their identifiable repeats and these sequences were compared using the Clustal method with weighted residue weight table (MegAlign software within DNASTAR sequence analysis package) to identify the relationship between the repeat sequences. Using this information, the ordering data provided by the RT-PCR, and sequence alignments (automatic and manual) using SeqMan (DNASTAR), one illustrative consensus full length O772P contig was identified comprising 20 distinct repeat units. The cDNA for this O772P cDNA contig is set forth in SEQ ID NO:569 and the encoded amino acid sequence is set forth in SEQ ID NO:595. This form of the O772P protein includes the following consensus repeat structures in the following order:

SEQ ID NO:572- SEQ ID NO:574- SEQ ID NO:575-SEQ ID NO:576-30 SEQ ID NO:577- SEQ ID NO:578- SEQ ID NO:589- SEQ ID NO:580- SEQ ID NO:581- SEQ ID NO:582- SEQ ID NO:583- SEQ ID NO:584- SEQ ID NO:585- SEQ 10

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WO 02/06317 PCT/US01/22635

ID NO:586- SEQ ID NO:587- SEQ ID NO:588- SEQ ID NO:589- SEQ ID NO:590- SEQ ID NO:591- SEQ ID NO:592- SEQ ID NO:593.

83

SEQ ID NO:595, therefore, represents one illustrative full-length consensus sequence for the O772P protein. As discussed above, however, based on current knowledge of this protein and based upon scientific literature describing proteins containing analogous repeating structures, many other forms of O772P are expected to exist with either more or less repeats. In addition, many forms of O772P are expected to have differing arrangements, e.g., different orders, of these N-terminal repeat structures. The existence of multiple forms of O772P having differing numbers of repeats is supported by Northern analysis of O772P. In this study, Northern hybridization of a O772P-specific probe resulted in a smear of multiple O772P-hybridizing transcripts, some in excess 10kb.

Thus, the variable repeat region of the O772 protein can be illustratively represented by the structure Xn - Y, wherein X comprises a repeat structure having at least 50% identity with the consensus repeat sequence set forth in SEQ ID NO:596; n is the number of repeats present in the protein and is expected to typically be a integer from 1 to about 35; Y comprise the O772P constant region sequence set forth in SEQ ID NO:594 or sequences having at least 80% identity with SEQ ID NO:594. Each X present in the Xn repeat region of the O772 molecule is different.

To determine the consensus sequences of each of the 20 repeat regions, sequences that were experimentally determined for a discrete repeat region were aligned and a consensus sequence determined. In addition to determining the consensus sequences for individual repeat regions, a consensus repeat sequence was also determined. This sequence was obtained by aligning the 20 individual consensus sequences. Variability of the repeats was determined by aligning the consensus amino acid sequences from each of the individual repeat regions with the over all repeat consensus sequence. Identity data is presented in Table 6.

<u>Table 6</u>

<u>Percent identities of Repeat Sequences with Reference to the Consensus Repeat Sequence</u>

Repeat Number	SEQ ID NO:	Percent Identity to
(amino acid)		Consensus Repeat
<u> </u>		Sequence
2	574	88
3	575	84
4	576	88
5	577	89
6	578	93
7	579	90
8	580	91
9	581	88
10	582	85
11	583	86
12	. 584	87
13	585	87
14	586	89
15	587	89
16	588	89
17	589	83
18	590	84
19	591	83
20	592	57
21	593	68

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration,

85

various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

86

CLAIMS

What is Claimed:

1. An O772P polypeptide having the structure:

 X_n-Y

wherein X comprises a sequence having at least 50% identity with the consensus O772P repeat sequence set forth in SEQ ID NO: 596;

Y comprises a sequence having at least 80% identity with the O772P constant region sequence set forth in SEQ ID NO: 594;

n is an integer from 1 to 35;

wherein each X present in said polypeptide is different.

- 2. The polypeptide of claim 1, wherein X comprises a sequence selected from the group consisting of any one of SEQ ID NOs: 574-593.
- 3. The polypeptide of claim 1, wherein Y comprises the sequence set forth in SEQ ID NO: 594.
 - 4. The polypeptide of claim 1, wherein n is an integer from 15 to 25.
 - 5. The polypeptide of claim 1, wherein n is 20.
- 6. The polypeptide of claim 1, wherein said polypeptide comprises SEQ ID NO: 595.
- 7. The polypeptide of claim 1, wherein said polypeptide is overexpressed in ovarian cancer cells compared with normal tissues.
 - 8. An O772P polypeptide having the structure:

 X_n-Y

87

wherein X comprises an O772P repeat sequence selected from the group consisting of any one of SEQ ID NOs: 574-593;

Y comprises a sequence having at least 90% identity with the O772P constant region sequence set forth in SEQ ID NO: 594;

n is an integer from 15 to 25;

wherein each X present in said polypeptide is different.

- 9. The polypeptide of claim 8, wherein n is 20.
- 10. The polypeptide of claim 8, wherein said polypeptide comprises SEQ ID NO: 595.
- 11. The polypeptide of claim 8, wherein said polypeptide is overexpressed in ovarian cancer cells compared with normal tissues.
 - 12. An O772P polypeptide having the structure:

 $X_{n}-Y$

wherein n is 20 and X comprises the following O772P repeat sequences:

SEQ ID NO: 574 - SEQ ID NO: 575 - SEQ ID NO: 576 - SEQ ID NO: 577 - SEQ ID NO: 578 - SEQ ID NO: 579 - SEQ ID NO: 580 - SEQ ID NO: 581 - SEQ ID NO: 582 - SEQ ID NO: 583 - SEQ ID NO: 584 - SEQ ID NO: 585 - SEQ ID NO: 586 - SEQ ID NO: 587 - SEQ ID NO: 588 - SEQ ID NO: 589 - SEQ ID NO: 590 - SEQ ID NO: 591 - SEQ ID NO: 592 - SEQ ID NO: 593; and

Y comprises the sequence set forth in SEQ ID NO: 594.

- The polypeptide of claim 12, wherein said polypeptide comprises 13. SEQ ID NO: 595.
- 14. The polypeptide of claim 12, wherein said polypeptide is overexpressed in ovarian cancer cells compared with normal tissues.

15. An O772P polynucleotide having the structure:

88

 X_n-Y

wherein X comprises an O772P repeat sequence selected from the group consisting of any one of SEQ ID NOs: 512-540, 542-546 and 548-567;

Y comprises a sequence having at least 95% identity with the O772P constant region sequence set forth in SEQ ID NO: 568;

n is an integer from 1 to 35;

wherein each X present in said polypeptide is different.

- 16. The polynucleotide of claim 15, wherein said polynucleotide comprises SEQ ID NO: 569.
 - 17. The polynucleotide of claim 15, wherein n is from 15 to 25.
 - 18. The polynucleotide of claim 15, wherein n is 20.
- 19. The polynucleotide of claim 15, wherein said polynucleotide is overexpressed in ovarian cancer cells compared with normal tissues.
- 20. An isolated polynucleotide comprising a sequence selected from the group consisting of:
 - (a) sequences provided in SEQ ID NOs: 464-477 and 512-569;
- (b) complements of the sequences provided in SEQ ID NOs: 464-477 and 512-569;
- (c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NOs: 464-477 and 512-569;
- (d) sequences that hybridize to a sequence provided in SEQ ID NOs: 464-477 and 512-569, under highly stringent conditions;
- (e) sequences having at least 75% identity to a sequence of SEQ ID NOs: 464-477 and 512-569;

- (f) sequences having at least 90% identity to a sequence of SEQ ID NOs: 464-477 and 512-569; and
- (g) degenerate variants of a sequence provided in SEQ ID NOs: 464-477 and 512-569.
- 21. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:
 - (a) sequences encoded by a polynucleotide of claim 20; and
- (b) sequences having at least 80% identity to a sequence encoded by a polynucleotide of claim 20; and
- (c) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 20.
- 22. An expression vector comprising a polynucleotide of claim 20 operably linked to an expression control sequence.
- 23. A host cell transformed or transfected with an expression vector according to claim 22.
- 24. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 21.
- 25. A method for detecting the presence of a cancer in a patient, comprising the steps of:
 - (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with a binding agent that binds to a polypeptide of claim 21;
- (c) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (d) comparing the amount of polypeptide to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.

26. A fusion protein comprising at least one polypeptide according to claim 21.

90

- 27. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:
 - (a) polypeptides according to claim 21;
 - (b) polynucleotides according to claim 20; and
- (c) antigen-presenting cells that express a polynucleotide according to claim 20,

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

- 28. An isolated T cell population, comprising T cells prepared according to the method of claim 27.
- 29. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of:
 - (a) polypeptides according to claim 21;
 - (b) polynucleotides according to claim 20;
 - (c) antibodies according to claim 24;
 - (d) fusion proteins according to claim 26;
 - (e) T cell populations according to claim 28; and
- (f) antigen presenting cells that express a polypeptide according to claim 21.
- 30. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 29.

WO 02/06317

91

PCT/US01/22635

- 31. A method for the treatment of a ovarian cancer in a patient, comprising administering to the patient a composition of claim 29.
- 32. A method for determining the presence of a cancer in a patient, comprising the steps of:
 - (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with an oligonucleotide that hybridizes to a polynucelotide sequence according to claim 21 under moderately stringent conditions;
- (c) detecting in the sample an amount of said polynucleotide that hybridizes to the oligonucleotide; and
- (d) comparing the amount of said polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence of the cancer in the patient.
- 33. An O772 polypeptide comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 490-511.
- 34. An O8E polypeptide comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 394-415.
- 35. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 1.

1/101

11729.1 contg

11729-45.21.21.cons1

11729-45.21.21.cons2

11731.1contig

TCTTTTCTTTCGATTTCCTCAATTTGTCACGTTTGATTTTATGAAGTTGTTCAAGGGCTAACTGCTGTGTAT
TATAGCTTTCTCTGAGTTCCTTCAGCTGATTGTTAAATGAATCCATTTCTGAGAGCCTTAGATGCAGTTTCTTTT
TCAAGAGCATCTAATTGTTCTTTAAGTCTTTTGGCATAATTCTTCCTTTTCTGATGACCTTTTTATGAAGTAAACT
GATCCCTGAATCAGGTGTGTTACTGAGCTGCATGTTTTTAATTCTTTCGTTTAATAGCTGCTTCTCAGGGACCA
GATAGATAAGCTTATTTTGATATTCCTTAAGCTCTTGTTGAAGTTGTTTGATTTCCATAATTTCCAGGTCACAC
TGTTTATCCAAAACTTCTAGCTCAGTCTTTTGTGTTTGCTTTCTGATTTTGGACATCTTGTAGTCTGCCTGAGAT
CTGCTGATGXTTTCCATTCACTGCTTCCAGTTCCAGGTGGAGACTTTXCTTTCTGGAGCTCAGCCTGACAATGC
CTTCTTGXTCCT

Fig. 1A

2/101

11731.2contig

11734.1contig

11734.2contig

GCCAAGAAAGCCCGAAAGGTGAAGCATCTGGATGGGGAAGAGGATGGCAGCAGTGATCAGAGTCAGGCTTCTGG
AACCACAGGTGGCCGAAGGGTCTCAAAGGCCCTAATGGCCTCAATGGCCCGCAGGGCTTCAAGGGGTCCCATAG
CCTTTTGGGCCCGCAGGGCATCAAGGACTCGGTTGGCTGCTTGGGCCCGGAGAGCCTTGCTCTCCCTGAGATCA
CCTAAAGCCCGTAGGGGCAAGGCTCGCCGTAGAGCTGCCAAGCTCCAGTCATCCCAAGAGCCTGAAGCACCACC
ACCTCGGGATGTGGCCCTTTTGCAAGGGAGGGCAAATGATTTGGTGAAGTACCTTTTTGGCTAAAGACCAGACGA
AGATTCCCATCAAGCGCTCGGACATGCTGAAGGACATCATCAAAGAATACACTGATGTGTACCCCGAAATCATT
GAACGAGCAGGCTATTCCTTGGAGAAAGGTATTTGGGATTCAATTGAAGGAAATTGATAAGAATGACCACTTGTA
CATTCTTCTCAGC

11736.1contg

3/101 11736.2contig

11739-1&2

11740.1.contig

Fig. 1C

4/101

11766.1.contig

11766.2.contig

11773.2.contig

11775-1&2

Fig. 1D

5/101 11777.1&2.cons

11779.2.contig

11781 & 37.cons

Fig. 1E

6/101 11781-76-87-37

11784-1 & 2

11785.2.contig

7/101 11718-1&2 cons

13690.4

CAACTTATTACTTGAAATTATAATATAGCCTGTCCGTTTGCTGTTTCCAGGCTGTGATATATTTTCCTAGTGGT
TTGACTTTAAAAATAAAGGTTTAATTTTCTCCCC

13693.1

13694.1

Fig. 1G

8/101

13694.2

GACTGTCCTGAACAAGGGACCTCTGACCAGAGAGCTGCAGGAGATGCAGAGTGGCAGGAGTGGAAGCCAAA GAACACCCACCTTCCTCCCTTGAAGGAGTAGAGCCAACCACCACCTTCCTCCCCTTGAAGGAGTAGAGCCAACCACCACCTCCCCCTTGAAGAGATACCAGAGATACTGTTTTATTGCTCTGGTCAAACAA GTCTTCCTGAGTTGACAACACCTCAGGCTCTGGTGACCTTGCAGACAACTGTTCTTTTGCTTCCATAGCAGCAACAGATGCTTTGGGGCTAAAAGGCATGTCCTCTGACCTTGCA GGTGGTGGATTTTGCTCTTTTACAACATGTACATCCTTACTGGGCTGTGCTGTCACAGGGATGTCCTTGCTGGA CTGTTCTGCTATGGGGATATCTTCGTTGGACTGTTCTTCATGCTTAATTGCAGTATTAGCATCCACATCAGACA GCCTGGTATAACCAGAGTTGGTGGTTACTGATTGTAGCTGCTCTTTTGTCCACTTCATATGGCACAAGTATTTTC CTCAACATCCTGGCACAG

13695.1

GAAATGTATATTTAATCATTCTCTTGAACGATCAGAACTCTRAAATCAGTTTTCTATAACARCATGTAATACAG
TCACCGTGGCTCCAAGGTCCAGGAAGGCAGTGGTTAACACACATGAAGAGTGTGGGAAGGGGGCTGGAAACAAAGT
ATTCTTTTCCTTCAAAGCTTCATTCCTCAAGGCCTCAATTCAAGCAGTCATTGTCCTTGCTTTCAAAAGTCTGT
GTGTGCTTCATGGAAGGTATATGTTTGTTGCCTTAATTTGAATTGTGGCCAGGAAGGGTCTGGAGATCTAAATT
CAGAGTAAGAAACCTGAGCTAGAACTCAGGCATTTCTCTTACAGAACTTGGCTTGCAGGGTAGAATGAANGGA
AAGAAACTTAGAAGCTCAACAAGCTGAAGATAATCCCATCAGGCATTTCCCATAGGCCTTGCAACTCTGTTCAC
TGAGAGATTATCCTG

13695.2

13697.1

TAGCTGTCTTCCTCACTCTTATGGCAATGACCCCCATATCTTAATGGATTAAGATAATGAAAGTGTATTTCTTAC ACTCTGTATCTATCACCAGAAGCTGAGGTGATAGCCCGCTTGTCATTGTCATCCATATTCTGGGACTCAGGCGG GAACTTTCTGGAATATTGCCAGGGAGCATGGCAGAGGGGCACAGTGCATTCTGGGGAATGCACATTGGCTCAG CCTGGGTAATGAGTGATATACATTACCTCTGTTCACAACTCATTGCCCAGCACCAGACCCAAATCCCAAGACCCCAAATGTAGTCCTGTTGATATGGTTTTTGCTGTGTCCCAACCCAAATCTCATCTTGAATTGT AAGCTCCCATAATTCCCATGTGTTGTGGGAGGGACCTGGTG

Fig. 1H

9/101

13697.2

13699.182

13703.3

13705.1

Fig. 1I

10/101

13705.2

13707.4

13708.182

GGCGGGTAGGCATGGAACTGAGAAGAACGAAGAAGCTTTCAGACTACGTGGGGAAGAATGAAAAAACCAAAATT
ATCGCCAAGATTCAGCAAAGGGGACAGGGAGCTCCAGCCCGAGAGCCTATTATTAGCAGTGAGGAGCAGAAGCA
GCTGATGCTGTACTATCACAGAAGACAAGAGGAGCTCAAGAGATTGGAAGAAAATGATGATGATGCCTATTTAA
ACTCACCATGGGCGGATAACACTGCTTTGAAAAGACATTTTCATGGAGTGAAAGACATAAAGTGGAGACCAAGA
TGAAGTTCACCAGCTGATGACACTTCCAAAGAGATTAGCTCACCT

13709.1

11/101 13709.2

TATGAAGAAGGGAAAAGAAGATAATTTGTGAAAAGAAATGGGTCCAGTTACTAGTCTTTGAAAAGGGTCAGTCTG
TAGCTCTTCTTAATGAGAATAGGCAGCTTTCAGTTGCTCAGGGTCAGATTTCCTTAGTGGTGTATCTAATCACA
GGAAACATCTGTGGTTCCCTCCAGTCTCTTTCTGGGGGGACTTGGGCCCACTTCTCATTTCATTTAATTAGAGGA
AATAGAACTCAAAGTACAATTTACTGTTGTTTAACAATGCCACAAAGACATGGTTGGGAGCTATTTCTTGATTT
GTGTAAAATGCTGTTTTTTGTGTGCTCATAATGGTTCCAAAAAATTGGGTGCTGGCCAAAGAGAGATACTGTTACA
GAAGCCAGCAAGAAGACCTCTGTTCATTCACACCCCCCGGGGATATCAGGAATTGACTCCAGTGTGTCAAAATCC
AGTTTGGCCTATCTTCT

13712.182

13714.1&2

13716.1&2

Fig. 1K

12/101

13718.2

13722.3

CATGCGTTTCACCACTGTTGGCCAGGCTGGTCTCGAACTCCTGGCCTCAAGCAATCCACCCGCCTCAGCCTCCA
AAAGTGCTGGGATTACAGATGTGAGCCATGGCACCATGCCAAAAGGCTATATTCCTGGCTCTGTGTTTCCGAGA
CTGCTTTTAATCCCAACTTCTCTACATTTAGATTAAAAAAATATTTTATTCATGGTCAATCTGGAACATAATTAC
TGCATCTTAAGTTTCCACTGATGTATATAGAAGGCTAAAGGCACAATTTTTATCAAATCTAGTAGAGTAACCAA
ACATAAAATCATTAATTACTTTCAACTTAATAACTAATTGACATTCCTCAAAAGAGCTGTTTTCAATCCTGATA
GGTTCTTTATTTTTTCAAAATATATTTGCCATGGGATGCTAATTTGCAATAAGGCGCATAATGAGAATACCCCA
AACTGGA

13722.4

13724-13698-13748

Fig. 1L

13/101

13730.1

13732.1

ATGGATCTTACTTTGCCACCCAGGTTGGAGTGCAGTGCTGCAATCTTGGCTCACTGCAGCCTTAACCTCCCAGG
CTCAAGCTATCCTCCTGCCAAAGCCTTCCACATAGCTGGGACTACAGGTACACNGCCACCCACACCCAGCTAAAA
TTTTTGTATTTTTTTGTAGAGACCGGGATCTCGCCACGTTGCCCAGGCTGGTCCCATCCTGACCTCAAGCAGATCT
GCCCACCTCAGCCCCCCAACGTGCTAGGATTACAGGCGTGAGCCACCCGCACCCAGCCTTTGTTTTGCTTTTAAT
GGAATCACCAGTTCCCCTCCGTGTCTCAGCAGCAGCTGTGAGAAATGCTTTGCATCTGTGACCTTTATGAAGGG
GAACTTCCATGCTGAATGAGGGTAGGATTACATGCTCCTGTTTTCCCGGGGGGTCAAGAAAGCCTCAGACTCCAGC
ATGATAAGCAGGGTGAG

13732.2

Fig. 1M

14/101

13735.1

13735.2

13736.1

13737.182

Fig. 1N

15/101 13738.1

TTTGACTTTAGTAGGGGTCTGAACTATTTATTTTACTTTGCCMGTAATATTTARACCYTATATATCTTTCATTA
TGCCATCTTATCTTCTAATGBCAAGGGAACAGWTGCTAAMCTGGCTTCTGCATTWATCACATTAAAAATGGCTT
TCTTGGAAAATCTTCTTGATATGAATAAAGGATCTTTTAVAGCCATCATTTAAAGCMGGNTTCTCCCAACACG
AGTCTGCTSASGGGGGGKGAGCTGTGAACTCTGGCTGAAGGCTTTCCCATACACACTGCAATGACMTGGTTTCT
GACCAGBGTGAGTTA

13738.2

13739.182

GAGACAGGGTCTCACTTTGTCACCCAGGCTGGAATGCAGTGGTGCGATCTTACGTAGCTCACTGCAGCCCTGAC
CTCCTGGACTCAAACAATTCTCCTGCCTCAGCCCTGCAAGTAGCTGGGACTGTGGGTGCATGCCACCATGCCTG
GCTAACTTTTGTAGTTTTTGTAAAGATGGGGTTTTGCCATGTTGCACATGCTGGTCTTGAACTCCTGAGCTCAA
ACGATCTGCCCACCTCGGCCTCCCAGAATGTTGGGATTACAGGGGTAAACCACCACGCCTGGCCCCATTAGGGT
ATTCTTAGCATCCACTTGCTCACTGAGATTAATCATAAGAGATGATAAGCACTGGAAGAAAAAAATTTTTACTA
GGCTTTGGATATTTTTTTCCTTTTTCAGCTTTATACAGAGAGTTAACCGGCATCACTCCCTTGCTCAATTCCAGTC
TTTACCACATCAATTATTTTCAGAGGTGCAGGATAAAGGCCTTTAGTCTGCACTTTTTCTTCCACTTT
TTTGTAAACCTGTTGCCTGACAAATGGAATTGACAGCGTATGCCATGACTATTCCATTTGTCAGCTG
TCAATTTTTCCACCAATCCCTTGTCTCTCTTTTGGAGAGAACCCCCTGGGACCAGGACTAAAACCTCCAG
GCAACTTCTTCTAGGTATTCTATTGTCCGTTCCCACTGGTGGAACCCCTGGGACCAGGACTAAAACCTCCAG

13741.1

Fig. 10

16/101

13742.1

14351.1

14351.2

ACCTTAAAGACATAGGAGAATTTATACTGGGAGAGAAAGCTTACAAATGTAAGGTTTCTGACAAGACTTGGGAG TGATTCACACCTGGAACAACATACTGGACTTCACACTGGABAGAAACCTTACAAGTGTAATGAGTGTGGCAAAG CCTTTGGCAAGCAGTCAACACTTATTCACCATCAGGCAATTCA

14354.2

AGTCAGGATCATGATGGCTCAGTTTCCCACAGCGATGAATGGAGGGCCAAATATGTGGGCTATTACATCTGAAG
AACGTACTAAGCATGATAAACAGTTTGATAACCTCAAACCTTCAGGAGGTTACATAACAGGTGATCAAGCCCGT
ACTTTTTTCCTACAGTCAGGTCTGCCGGCCCCGGTTTTAGCTGAAATATGGGCCTTATCAGATCTGAACAAGGA
TGGGAAGATGGACCAGCAAGAGTTCTCTATAGCTATGAAACTCATCAAGTTAAAGTTGCAGGGCCAACAGCTGC
CTGTAGTCCTCCCTCCTATCATGAAACAACCCCCTATGTTCTCCCACTAATCTCTGCTCGTTTTTGGGATGGGA
AGCATGCCCAATCTGTCCATTCATCAGCCATTGCCTCCAGTTGCACCTATAGCAACACCCTTGTCTTCTGCTAC
TTCAGGGACCAGTATTCCTCCCTAATGATGCCTGCT

14354.1

Fig. 1P

17/101 16431.1.2

16432-1

16432-2

17184.3

Fig. 1Q

18/101 17184.4

CAAGCGTTCCTTTATGGATGTAAATTCAAACAGTCATGCTGAGCCATCCCGGGCTGACAGTCACGTTWAAGACA CTAGGTCGGGCGCCACAGTGCCACCCAAGGAGAAGAAGAATTTTGGAATTTTTCCATGAAGATGTACGGAAATCT GATGTTGAATATGAAAATGGCCCCCAAATGGAATTCCAAAAGGTTACCACAGGGGCTGTAAGACCTAGTGACCC TCCTAAGTGGGAAAGAGGAATGGAGAATAGTATTTCTGATGCATCAAGAACATCAGAATATAAAACTGAGATCA TAATGAAGGAAAATTCCATATCCAATATGAGTTTACTCAGAGACAGTAGAAACTATTCCCAGG

17185.1

TAGGAATAACAAATGTTTATTCAGAAATGGATAAGTAATACATAATCACCCTTCATCTCTTAATGCCCCTTCCT
CTCCTTCTGCACAGGAGACACAGATGGGTAACATAGAGGCATGGGAAGTGGAGGAGGACACAGGACTAGCCCAC
CACCTTCTCTCTCCCGGTCTCCCCAAGATGACTGCTTATAGAGTGGAGGAGGCAAACAGGTCCCCTCAATGTACCA
GATGGTCACCTATAGCACCAGCTCCAGATGGCCACGTGGTTGCAGCTCGACTCAATGAAACTCTGTGACAACCA
GAAGATACCTGCTTTGGGATGAGAGGGAGGATAAAGCCATGCAGGAGGATATTTACCATCCCTACCCTAAGCA
CAGTGCAAGCAGTGAGCCCCCGGCTCCCAGTACCTGAAAAAACCAAGGCCTACTGNCTTTTGGATGCTCTCTTGG
GCCACG

17188.2

17190.1

19/101

17190.2

17191.2889.2

20/101

AGCCAGATGGCTGAGAGCTGCAAGAAGAAGTCAGGATCATGATGGCTCAGTTTCCCACAGCGATGAATGGAGGG CCAAATATGTGGGCTATTACATCTGAAGAACGTACTAAGCATGATAAACAGTTTGATAACCTCAAACCTTCAGG AGGTTACATAACAGGTGATCAAGCCCGTACTTTTTTCCTACAGTCAGGTCTGCCGGCCCCGGTTTTAGCTGAAA TATGGGCCTTATCAGATCTGAACAAGGATGGGAAGATGGACCAGCAAGAGTTCTCTATAGCTATGAAACTCATC ACTAATCTCTGCTCGTTTTGGGATGGGAAGCATGCCCAATCTGTCCATTCATCAGCCATTGCCTCCAGTTGCAC CTATAGCAACACCCTTGTCTTCTGCTACTTCAGGGACCAGTATTCCTCCCCTAATGATGCCTGCTCCCCTAGTG CCTTCTGTTAGTACATCCTCATTACCAAATGGAACTGCCAGTCTCATTCAGCCTTTATCCATTCCTTC TTCAACATTGCCTCATGCATCATCTTACAGCCTGATGATGGGGAGGATTTGGTGGTGCTAGTATCCAGAAGGCCC AGTCTCTGATTGATTTAGGATCTAGTAGCTCAACTTCCTCAACTGCTTCCCTCTCAGGGAACTCACCTAAGACA GGGACCTCAGAGTGGGCAGTTCCTCAGCCTTCAAGATTAAAGTATCGGCAAAAAATTTAATAGTCTAGACAAAGG CTACTATTTGGACTCTGGCTGACATCGATGGTGACGGACAGTTGAAAGCTGAAGAATTTATTCTGGCGATGCAC CTCACTGACATGGCCAAAGCTGGACAGCCACTACCACTGACGTTGCCCCCGAGCTTGTCCCTCCATCTTTCAG AGGGGGAAAGCAAGTTGATTCTGTTAATGGAACTCTGCCTTCATATCAGAAAACACAAGAAGAAGAAGACCCCAGA AGAAACTGCCAGTTACTTTTGAGGACAAACGGAAAGCCAACTATGAACGAGGAAACATGGAGCTGGAGAAGCGA GAAACAGAGAACTGCAAGAGCAAGAATGGAAGAAGCAGCTGGAGTTGGAGAAACGCTTGGAGAAACAGAGAG CATTGTCAGGCTGAGCTCCAGAAAGAAAAGTCTCCACCTGGAACTGGAAGCAGTGAATGGAAAACATCAGCAGA TCTCAGGCAGACTACAAGATGTCCAAATCAGAAAGCAAAACACAAAAGACTGAGCTAGAAGTTTTGGATAAACAG GGTCCCTGAGAAGCAGCTATTAAACGAAAGAATTAAAAACATGCAGCTCAGTAACACCCTGATTCAGGGATCA GTTTACTTCATAAAAAGTCATCAGAAAAGGAAGAATTATGCCAAAGACTTAAAGAACAATTAGATGCTCTTGAA AAAGAAACTGCATCTAAGCTCTCAGAAATGGATTCATTTAACAATCAGCTGAAGGAACTCAGAGAAAGCTATAA TAGAGCAAAAAAAAAAAA

21/101

ATGGCAGTGACATTCACCATCATGGGAACCACCTTCCCTTTTCTTCAGGATTCTCTGTAGTGGAAGAGAGCACC CAGTGTTGGGCTGAAAACATCTGAAAGTAGGGAGAAGAACCTAAAATAATCAGTATCTCAGAGGGCTCTAAGGT GCCAAGAAGACTCTCACTGGACATTTAAGTGCCAACAAAGGCATACTTTCGGAATCGCCAAGTCAAAACTTTCTAA CTTCTGTCTCTCTCAGAGACAAGTGAGACTCAAGAGTCTACTGCTTTAGTGGCAACTACAGAAAACTGGTGTTA CCCAGAAAAACAGGAGCAATTAGAAATGGTTCCAATATTTCAAAGCTCCGCAAACAGGATGTGCTTTCCTTTTGC CCATTTAGGGTTTCTTTTTTTTTATTAACCACTA

22/101

ATATCTAGAAGTCTGGAGTGAGCAAACAAGAGCAAGAACAAAAAGAAGCCAAAAGCAGAAGGCTCCAATATGA ACAAGATAAATCTATCTTCAAAGACATATTAGAAGTTGGGAAAATAATTCATGTGAACTAGACAAGTGTGTTAA GGAGTGAGAGGACAGGATAGTGCATGTTCTTTGTCTCTGAATTTTTAGTTATATGTGCTGTAATGTTGCTCTGA GGAAGCCCCTGGAAAGTCTATCCCAACATATCCACATCTTATATTCCACAAATTAAGCTGTAGTATGTACCCTA AGACGCTGCTAATTGACTGCCACTTCGCAACTCAGGGGCGGCTGCATTTTAGTAATGGGTCAAATGATTCACTT TTTATGATGCTTCCAAAGGTGCCTTGGCTTCTCTCCCAACTGACAAATGCCAAAGTTGAGAAAAATGATCATA ATGCGGGTTTATTTCTCAGATGATGTTCATCCGTGAATGGTCCAGGGAAGGACCTTTCACCTTGACTATATGGC ATTATGTCATCACAAGCTCTGAGGCTTCTCCTTTCCATCCTGCGTGGACAGCTAAGACCTCAGTTTTCAATAGC ATCTAGAGCAGTGGGACTCAGCTGGGGTGATTTCGCCCCCCATCTCCGGGGGAATGTCTGAAGACAATTTTGTT ACCTCAATGAGGGAGTGGAGGATACAGTGCTACTACCAACTAGTGGATAAAGGCCAGGGATGCTGCTCAAC CTCCTACCATGTACAGGACGTCTCCCCATTACAACTACCCAATCCGAAGTGTCAACTGTGTCAGGACTAAGAAA GGCAAATAAGCATTCTGTCTCTTTGGCTGCCTCAGCACAGAGAGCCAGAACTCTATCGGGCACCAGGATAA CATCTCTCAGTGAACAGAGTTGACAAGGCCTATGGGAAATGCCTGATGGGATTATCTTCAGCTTGTTGAGCTTC TAAGTTTCTTTCCCTTCATTCTACCCTGCAAGCCAAGTTCTGTAAGAGAAATGCCTGAGTTCTAGCTCAGGTTT TGAAGCACACACAGACTTTTGAAAGCAAGGACAATGACTGCTTGAATTGAGGCCTTGAGGAATGAAGCTTTGAA GGAAAAGAATACTTTGTTTCCAGCCCCCTTCCCACACTCTTCATGTGTTAACCACTGCCTTCCTGGACCTTGGA GCCACGGTGACTGTATTACATGTTGTTATAGAAAACTGATTTTAGAGTTCTGATCGTTCAAGAGAATGATTAAA TATACATTTCCTA

23/101

Flement Displa	play					:	:				800
Office	Plobe 1	59	Probe 2	C GENZEBINEK	FINANT.	Probe 1	5.A A.S	Probe 1 S.P. 43 Probe 2	S/8 42	42	157.1
*1.7 384A Ove	Overy T (mets)	() ()	272A Deridrific cells	42240808 (420)	4210019B (C-11)	2393	13.4 6	59 1430	2.0	S	
335A. OV	Ovary		Sr Ovary'N	42220626 (420)	42/00/98(011)	355	2.7 5	54 382	1,8	¥	:
+1.8 261A QV	Ovary T	療	SID Skeletal muscle N	4223062H (420)	42160196 (C-11	1298	8.8	St 707	1.9	57	: .
+8.1 284A Ovs	Overy T		S2 Pancreas N	422ND829 (430)	42100/3B (C1)	9590	44.0 62	2.1 (180	153	8	
-1.2 386A Over	yT		S40: PBMC (sictiVated)	422,01605 (420)	न्यात्कोकादानः िग्रह	516	3.8	50 819	SΩ	8	
+4.7 285A-Ov	Ovary T	5	CTS Hear N	42200624 (420)	कारकाञ्च (८११) ४३०६	2305	14.8 53	3 488	22	8	
-1.4 S25 Ova	Vary T		CT4 Bont Marrow N	422HD619 (420)	42100188[C11.	831	35 6	53 743	2.0	ន	
383A OVE	ry T (rhets)	2	"II COLOTIN	42280609 (420)	42100198.(C11"	1842	10.6 39	1/29	20	8	
-119 S22 Over	Wary T.		CT9 Kidney N	42290627 (420)	42100196 (c.11)	£33	89 66	8 857	32	8	
+3.2 8485.OT	NT-1-P (SCID)	盘	(8485 OF 5-P (SCID)	422Y0602 (420)	(-421c0186 (C.11;)	1862	12: 57	785	23	15	
+1.5 Z62A OVE	Qvary T	· ·	334A, Large Integline N	422A0622 (420)	42160198,(C11)	1488	7.5 55	5 965	22	જ	•
-1.1 S115 Over	y T(mets)	显	CT10 Small Intestine N	422C0604 (420)	42100196 (C11)	508	3.4 51	513	50	ফ	
+1.1 ZBBA OVB	QV&ry T		-G112 Lung N	422¥0625 (420)	42100196 (C11;)	7007	4.5 54	4 (851	2.1	8	••
-2.1 (2014 QV	QvaryT		S6 Stemach N	422V0620 (420)	42160198 (C.11.)	97.9	4.5 46	335	3.6	46	
+7.8 S23 Over	/ ١	Ç.	SS6 Spinal Cond N	42250626 (420)	42100196 (C.11.)	3836	22. 50	505	2.2	8	
+1:8 205A Ova	ıy T	មា	270A. Liver N	42200606 (420)	421GD19B (C:11]	2251	14.7 46	5 1256	20	\$	
1.9 S334 Ove	Wary T (SCID)		IZ Skin N	422R0801 (420)	42100198 (C11.	552	3.4 72	2 1029	23	2	
+5.6 385A OVE	Overy T	2 (2)	Sgi fetaltissue	422X0607 (420)	42190139 (C11	87.18	35.6	1449	20	ន	
35 2834 OV	Ovary T		S73 Breast N	422H0623 (420)	42/100/98 (C11)	83.	3.2 6	1531	3.4	<u>8</u>	
-3:3 382A Ove	7 VribyC		CT19 BrainN	42200610 (420)	42100198 (C11	387	3.2 50	1278	21	8	
+4.B 286A Over	Overy T	Ē	S27 Ovary N	42250609 (420)	42160198.(C-11.	4242	22.58	58 83	20	B	
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rig. 3

24/101

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27/101

Fig. 7A

AGCGTGGTCGCGGCCGAGGTCCAGTCGCAGCATGCTCTTTCTCCTGCCCACTGGCACAGTGAGGAAGATCTCTG CTGTCAGTGAGAAGGCTGTCATCCACTGAGATGGCAGTCAAAAGTGCATTTAATACACCTAACGTATCGAACAT CATAGCTTGGCCCAGGTTATCTCATATGTGCTCAGAACACTTACAATAGCCTGCAGACCTGCCCGGGCGGCCGC TCGA

Fig. 7B

28/101

29/101

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· œ	AK	જ	æ	12	5	æ	8	75	6	₩.	8	80	8	.00	5	86	S	8	8	83	8	ક	88	87	8
Probez	8/8	27	G.E.	7 8	1.6		9	2.1	23	5.6	2,9	27.	表	30	9.5	60	20	6.4	77	4.0 0:4	굓	23.9	23	e, e,	325
Xe1	A%	8	&	Ę	E.	\$	8	ĸ	8		8	8	B.	951	6	8	S	6	6	8	8	S	88	85	8
Probe1	B/B	57.7	35,3	Ķ	G G	39.2	20.4	S	23.0	38.5	14.0	10.4	(3.9	86	161	30.4	<u> </u>	11.0	230	991	9.6	22,0	10.9	10.7	ė,
Probe2	Value	1240	000	2121	1480	21.16	1113	8.4	127	3536	1081	166	904	8 17	34.80	3653	1274	1072.	3074	210	1297	2084	1663	1473	1204
Probet	Value	0298	\$85 885	12151	7487	7302	37.14	2435	4578	286	2191	61,61	161	1666	1827	5914	2039	1736	4204	3000	1643	2521	2072	1840	1329
GEM	Į.	42200606	IN 422GU628	422X0607	422X0611	422HD623	422B0609	422R0601	cl142240608	422ND629	var422/70605	str 422C0604	42200624	42220626	N42240612	\$HM2230621	42250603	42290627	3D422X0602	stir422A0622	w 422H0619	42210614	42200610	422V0625	4225V0620
Probe 2	ame	270A Liver N	S56 Spinal Core	SOI Fetal tissue	415A Aorta N	S73 Break N	Il Colon N	IZ Skin N	272A Dendritie	S2 Pancreas N	S40 PBMC (act	CT10 Small inte	CTS Heart N	S7 Ovary N	243A Esoplago	\$10. Skeletal mu	SZZ Ovary N	CT9 Kidney N 42	9485 OT 5-P (SC	334A Large Intestité	CT4 Bone Marr	364X Overy'N	T19 Brain N	-	S6 Stornach N.
44	P2 N		्र १३ ० मा		· 注理				e FAE	€ } }			, , , ,		0	44			<u> </u>	C FR		0			
		THE STATE OF THE													100000			THE TOTAL PROPERTY.						A THE CONTRACTOR	TOTAL STREET
Bal Probe 1	Erip Name P1	17.0 205A Ovary T	. 5	+5.7 385A OvaryT	+5.1 426A Ovary T (mets #	43.5 263A Ovary T	+3.3 383A Ovary T (med. 13)	ary T (SCIL	+2.6-384A Overy T (mete (3)	ary T	+2.0 386A Ovary T	ury T (mets	+2,0 265A OvaryT	+2,0 335A Ovary T	dry T (met)	+1.6 261A Ovary T	art.	+1.6 \$22 Ovary T.	M 1-P (SCID	262A Overy T	\$25 Overy T	#12. 429A Ovary T (men 🔄	382A Ovary: T	288A O	201A Ovary T
Bal	क्रम्ब	1.7.0	5.54	+5.7	+5:1	43.5	+33	+3.0	+2.6	+22	120	+20	+20	+20	-19	+1.6	+1.6	+1.6	林(4)	+1.4	£1.4	#17	+1.2	+17	1.1+
Сепе	Name	(£CI) 88100174:	42 (00138 (103)	42100188 [173]	42100188 (D3)	42100188 (D3)	42100188 (D3)	42100188 (D3)	42100188 (D3)	42100188 (D3)	42100188 (D3)	42 (OD188 (D3)	42100188 (D3)	42100188 (D3)	42100188 (103)	42100188 (D3)	42100188 (D3)	42100188 (D3)	42100188 (D3)	42100188 (D3)	42100188 (D3)	42100188 (103)	42100188 (D3)	42100188 (D3)	42100188 (D3)

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	A&.	54	. 89	9	£3	. 89	.	.	9	89	9	68	5	97	Š.	2	20	69	, S.	6		75	33	95.	24
Probez	8/19	20	3.0	5,6	2.3	女女	2.1	3.6	7.4	3.6	51	0.	3.9	7.7	2.1	6	2	ຊ		00 66	6.	26	3,7	2.4	<u>,</u>
190	24	ま	89	61	đ,	89	\$	æ	3	8	8	89	2	\$	ġ	2	8	83	3	8	প্র	75	3	38	*
Probe.	8/8	103.3	633	67.3	93.1	58.2	24.5	40.9	226	39.5	11.6	19.2	S.	143	4	41.5	6.2	16		16.8	42	3.7	, ,	4.5	6.8
Proba2	Value	1424	1179	1273	1488	2235	1424	2245	638	1949	607	1293	1276	1260	.837	3726	1471	1054	1243	2214	4	250	.1237	797	862
Probei	value	26711	13559	14125	16121	11326	6583	9865	2803	8271	2281	3192	565	2774	1774	6967	2313	1657	848	3171	83	592	1197	3	4470
CEEN	TD.	422X0607	422G0628	422X0611	42200606	422H0623	42240608	422N0629	42210614	42230621	1422030604	42200624	42290627	42250603	422R0601	422Y0602	42200610	422V0625	422H0619	H22A0622	142210605	42220626	422W0620	42240612	422B0609
Probe 2	P1 P2 Name	Sol Fetal tissue	S56 Spinal Cord N	415A Aorta N	D Z70A Liver N	S73 Breast N	5 272A Denduite oells	S2 Pancress N	364A Ovary N	S 10 Steleral muscle b	CT10 Small intestine	Z CTS Heart N	CT9 Kidney N	S27 Ovary N	- I2 Skin N	9485 OT 5-P (SCID)	CT19 Brain'N	CT12 Ling N	CT4 Bone Marrow N	334A Large Intestine	S40 PBMC (netlyated	S7 Overy N	S6 Stornach N	A 243A Esophagus N	II Colon N
Bal Probe 1	Name	418.8 385A Ovary T		+11.1 426A Ovary T (mess)		+5.1 263A Ovary T		264A	44.4.429A Ovary T (mets)		+3.8 -S115 Ovary T-(mets)	12.5-265A Ovary T	-2.3 S22 OvervT	+2.2 266A Ovary T	+2.1 9334 Ovary T. (SCID)	~	+1.6 382A Ovary T	+1.6 288A OvaryT	-1.5 SZ5 OVRNYT	+1.4 262A Ovary T:	+1.2:386A Ovary T	-1.2 335A Ovary T	-1.0 201A Ovary T	-1.0 428A Overy T (mcts) -	383A Ovary T. (mets)
Gene	Name	421B0181/fC31	49.180181 (C3)	421B0181 (C3)	421R0181 (C3)	.421B0181 (C3)	421B0181 (C3)	421B0181-(C3)	421B0181 (C3)	42110181 (C3)	421B0181 (C3)	42 (B0181, [C3])	421B0181-(C3)	421B0f81 (C3)	421B0181 (C3)	421B0181 [C3]	421B0181 (C3)	421B0181 (C3)	421B0181 (C3)	421B0181 (C3)	421B0181 (C3)	421B0181 (C31		421B0181 (C3)	42/B0/81 (C3)

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22	18.8	75	.	.4 .	23	4	4	.	7	웊	8	٤,	7	69	Ç.	8	81	58	52	62	9	09	99	3	62
Prob	3/B	3.5	<u>«</u>	2.2	34	2.2	4.	6.7.	<u>6</u>	9:0	5.1	7.7	3:6	च ला	2,2	23	3.5	ei ei	et m	긺	Ä	22		c;	32
18	AR	7.75	4	⇔	73	÷	*	9	7	8	8	હ	4	3	\$	8	81	28	73	25	8	\$	\$	S	62
Prof	8/B	46.3	61.2	62	47.3	27.6	57.	20.3	38.8	3.5	34.6	خ. م	12.7	e N	18.7	2	13.6	7.0	13.2	3.0	23	er)	21.5 21.5	7.	7.4
Probe2	Value	462	S	1459	88	748	6061	543	22.74	1375	3245	738	11.13	88	1267	1330	1080	8,47	1651	738	1120	261	3529	689	1018
Probe1	Value	7706	10171	14415	1811	4807	9815	2661	7934	480	8003	1864	2552	386	3516	8	2063	1550	2559	534	893	46	4188	225	1008
GEM	A	422X0611	42200606	422X0607	N 422G0628	422B0609	422H0623	42210614	422N0629	× 422H0619	142230621	in 422C0604	422R0601	42290627	1142240608	42200610	42200624	42250603	Jr422A0622	ary 22, 1060, 5	422V0625	42220626	D422Y0602	N42240612	422W0620
robe 2	Name	415A Aorta N	270 Liver N	S91 Fetal dispue	S56 Spinal Cord	Il Colon N	S73 Bream N	364A Ovary N	S2 Pancreas N	T4 Bone Marro	S 10 Skeletal muscled 223062	T10 Small intest	2 Skin N	T9 Kidney N.	272A Dendritic ce	CTI9 Brain N	CIS Heart N	S27. Ovary N	334A Large Intest	S40 PERMC (north	TI2 Lung N	ST OWER N	485 OT 5-P (SCI	243A Esoplugus	36 Stornach N
	P2 N								The state of the s			17411	- Investor					The state of the s					2 0		
	E.				G	(a)		1 S																1 CHINE	
Bal Probe 1	EXD Name	+16.7 426A Ovary T (me	0.7 205A Ovary T	385A Ovary T	8.8 \$23 Overy T	6.4 383A Ovary T (mo	5.1 263A Ovary T	4.9 429A Ovary T (me	3.5 264A Ovary T	2.9 S25 Ovary T	2.8 26TA Ovary T	2.5 S115 Ovary T (met	2.3-9334 Ovary T (SCI	2.3 S22 Ovary T	2.2 384A Overy T (me)	22 3824 Ovary T	1.9-265A Ovary T	1.8 266A Ovary T	1.5 262A Ovary T	1.4 386A Ovary T	1.3 288A Oviny T	1.3 335A Ovary T	1.2 9485-OT 1-P (SCIL	1.1 428A Ovary T (moi	-1.0 201A Ovary T
Gerie.		42110182-(147): +1			(H)	(H7)	H.3			421T0182 (147)						42110182 (H7)	H	٠.	Œ		42110182 (HT)	42J10182 (H7-)	Œ	42110182 (H7) +	HJ:)

Gene	Bal Probe 1		Probe	73 :	GEN	Proba1	Probe2	Probei	10	Probe2	62
Neme	Exp Name P1		P.2. Neme		ę,	Value	value.	S/B	F. 18	S/B	2
421V0189 (DL)	+33.2, 426.4 Overy T (mets	The state of the s	4154	Aorta N	422X061j	8072	8	55.2	. 19	24	19
421V0189 (DI)	+13.7-523.0vary T		\$58	Spinal Cord P	V 422G0628	7367	237	42.6	9	2.5	3
421 X0189 (DL)	+12.6.429A Ovary T (mes	The Contract of the State of th	36AA	Overy'N	42Zlb614	2850	Z	21.7	Z	3.5	3
421V0189 (IDI)	+8.0, 385.A. Overy T		.291	Fetal tissue	422X0607	11711	1469	¥.	00	22	\$ 5 ,
421V0189 (DI)	47.3 263A Ovary T		573	Breast N	42ZHD623	8	22	37.8	8	9.	3
421V0189 (D1)	-5.8.525 Ovary T		ţ	CT4 Bone Minns	v 422H0619	802	1210	2.1	4	2.0	4
421VQ189 (D1)	45.0 205A Ovary T		2704	LiverN	42200606	8676	1737	523	Ş.	2.6	Ŋ.
42 I VOI R9 (D1)	83A		Ŭ ≒	I Colon N	422B0609	3149	707	17.4	27	70	57
421V0[89 (D1)	44.4 261A Ovary T		810	S10 Skeletal musc	142230621	6332	1443	29.1	7	ဂ	F
42 [VO] R9 [D1]	+4.2 264A Overy T		S2 P	52 Panoreas N	422N0629	7612	1809	38.1	2	i,	8
421V0189 (DJ)	-3.2.382A Overy T		Ç	T19 Brain N	42200610	468	1508	3.4	8	23	8
421V0189 (DT)	+2:9 9334 Overy T (SCIL ®		IP.SK	P. Skin N	422R0601	2500	.098	123	۲	2.1	3
421V0189 (DJ)	+2.5 Si15 Ovary T (mots-		CTIC	T10 Small intesti	n422C0604	1424	283	6.7	2	7	4
421V0189 (TD1)	+2.4 265A Ovury T	California Option (Car	CIS	TIS Heart N	42200624	1742	7,23	8.	2	2.8	5
421V0189 (D)	+2.3 384A: Ovary T (metr	Activities Contaction	272	Dendritie eel	1142240608	3083	1342	17.0	29	2.0	3
421V0189 (D1)	+1.9 266A Ovary T		\$27.0	Ovary.N	42250603	1370	732	0.8	47	2.0	4
421V0189 (D1)	-1.9 386A Ovary T	Chemistra Printers	.S.40	PBMC (active	1142210605	307	280	2.6	₹	50	₹
421V0189 (D1)	41.7 262A Ovary T		334	Large Intest	ir422A0622	2097	25 25	11.2	8	53	8
421V0189 (D1)	-L3 335A, Ovary T	Language Companies	S	Ovary.N	42220626	373	470	2.9	4	20	4
421V01897(D1)	-1.1. 288A Ovary T.	Control of the last of the las	כל	Lung	42200625	696	1691	5.6	22	20	2
421 V0189 (D1)	+1.1 201A Ovary T	THE STATE OF THE PARTY OF THE P	\$6.5	6 Stornach N	422W0620	750	229	2.6	8	çi Çi	g
421 you 89 (DJ)	+1.1 4284 Ovary I (mets.	ATTEN THE PERSON	Acto	243A Esophague 7	V42240612	498	\$	4.2	E.	긺	82
421V0189 (D1)	-1.0 9485 OT 1-P (SCID-12)	THE PROPERTY OF THE PARTY OF TH	9485	OT S-P (SCII	2422Y0602.	31.17	31.74	16.7	20	8.5	5
421V0189 (DI)	\$22. Overy T	Transport Transport	B	Kidney N	42290627	224	4 09	23	8,	23	₹

FIQ. 13

		•									•														
pe2	A.	ጽ	Š	SS	4 5	S	48	£18	25	B	4	8	4	SI	42	4	ଝ	3	78	5 5	58	.57	89	.9	₹.
Pro	8/8	2.3	2.3	2.5	7	2.0	2.0	20	is.	9	7.1	3:0	61	25	50	2.2	2.6	2.6	<u>6</u> 1	20	2,3	6.0	12	22	22
bei	. A.S.	ટ	35	8	. 5	:S	84	\$	χ,	8	4.	\$	\$.	25	47	4	S	. 29	8	8	88	2	88	<u>%</u>	4
Probe	6/B	36.3	27.1	10.1	33.8	31.1	11.9	2.6	17.7	,23,0	x	14.9	13.4	4	3,7	52	10:T	4	2.7	2	<u>5</u>	15.1	125	7:6	27
Probe2	Value	270	533	55	1668	1235	438	1259	1036	1239	627	9	1270	53	683	98	1245	800	328	50	677	2493	262	596	845
Probel	Value	5441	23.8	1252	9507	5456	- ES	8	3733	4163	585	3455	2667	291	410	1622	1892	Ş	55 57	382	558	2582	1922	1739	283
GER	TD	422X061.1	N 422GD628	42210614	422X0607	42200606	42200624	42200610	scl42230621	422H0623	tin422C0604	422N0529	e1142240608	42290627	vara2210605	422RD601	ctir422A0622	422 V0625	N42240612	42220626	422W0620	ID422Y0602	422B0609	42250603	w 422H0619
Probe 2	Name	415A Agma N	S56. Spinal Cord	364A Owary N	S91 Fetal tissue	270A Liver N	CTS Heart N	CT19 Brain N	S10 Skeletal mu	S73 Breast N	CT10 Small intes	SZ Punctons N	272A Dendritic e	Cro Kidney N	S40 PBMC (activ	12 Skin N	334A Large Inter	CT12 Lung N	243A: Esophagus	S7 Overs N	S6 Stornach N	9485 O'T 5-P (SC	II Colon N	S27 Ovary N	CT4 Bone Marro
	P2			206		risia)			. •	: : :		Z E) 0 m	: (100	o i	, i		· 1			in in	Ş.			
• - -		TATAL TATAL		CANTON SECOND				TATAL TOTAL	Herogram Caram		THE PARTY OF THE PARTY.	The Fig. 1. The Party of Street, Stree	والمعربة المورادج الأو		TOTAL TOTAL					The state of the state of	TOWNSHIP OF THE STREET		STRITONO STREET		
Bal Probe 1	Exp Name P1	+20.2 426A Ovgry T (metr 2)	+100 S23 Ovary T	+8.3 429 A Ovary T (mets	+5.7 385A Ovary T	+4.4 205A Overy T	+4.2 265A Ovary T	-4.1.382A Overy T	+3.6 261A Ovary T	+3.4.263.A. Oyacy T	+25 S115 Ovary T (mets a	+2.1. 264A Ovany T	+2.1 384 A. Ovary T (mes ex	-2.1 S22 Ovary T	-1.7 386A Ovary "	+1.6 9384 Ovary T (SCIT &	+1.5 262A Ovary T	-1.5.288A. Ovary T.	-1.4 428A Ovary T (mets.	-1.3 335A Ovary T.	-1.2 201A Ovary T	+1.0 9485 OT 1-P (SCID P	383.A. Oyary T' (metrical)	266A. Ovnry T	\$25 Owary T
Gene	Name	421H0187 [B11]	421H0187 (BI1)	421H0187 [B11]	421H0187 [E11]	421H0187 (E11)	421H0187 (E11)	42JE0187 (E11)	421H0187-(E11)	421HD[87 (E11)	421H0187 (E11)	421H0187 (EL1)	42'HO187 [E111	421H0187 (EUT)	2 UHO187 (E11)	421H0187 (E11)	42(H0(87 (E11)	42.[B0[87 (E)1)	42.IH0187 (E11)	42110187 (E11)	421H0187 [L11]	421H0187 [E11]	421H0187 (E11)	42:H0187-[E[1]	42 [HO187 [E11]

FIG. 14

35/101

11721-1

11721-2

AAGGCTGGTGGGTTTTTGATCCTGCTGGAGAACCTCCGCTTTCATGTGGAGGAAGAAGGGAAAGATGC
TTCTGGGAACAAGGTTAAAGCCGAGCCAGCCAAAATAGAAGCTTTCCGAGCTTCACTTTCCAAGCTAGGGGATG
TCTATGTCAATGATGCTTTTTGGCACTGCTCACAGAGCCCACAGCTCCATGGTAGGAGTCAATCTGCCACAGAAG
GCTGGTGGGTTTTTGATGAAGAAGGAGCTGAACTACTTTGCAAAGGCCTTGGAGAGCCCAGAGCGACCCTTCCT
GGCCATCCTGGGCGAGCTAAAGTTGCAGACAAGATCCAGCTCATCAATAATATGCTGGACAAAGTCAATGAGA
TGATTATTGGTGGTGGAATGGCTTTTACCTTCCTTAAGGTGCTCAACAACATGGAGATTGGCACTTCTCTGTTT
GATGAAGAGGGAGCCAAGATTGTCAAAGACCTAATGTCCAAAGCTGAGAAGAATGGTGTGAAAGATTACCTTGCC
TGTTGACTTTGTCACTGCTGACAAGTTTGATGA

11724-1

11724-2

Fig. 15A

36/101 11725-32-1.2

11726 - 182

11727-182

Fig. 15B

37/101 11728.1.40.19.19

11728.2.40.19.19

CCCGTGGGTGCCATCCACGGAGTTGTTACCTGATCTTTGGAAGCAGGATCGCCCGTCTGCACTGCAGTGGAAGC
CCCGTGGGCAGCAGTGATGGCCATCCCCGCATGCCACGGCCTCTGGGAAGGGGCCAGCAACTGGAAGTCCCTGAG
ACGGTAAAGATGCAGGAGTGGCCGGCAGAGCAGTGGGCATCAACCTGGCAGGGGCCACCCAGATGCCTGCTCAG
TGTTGTGGGCCATTTGTCCAGAAGGGGACGGCAGCAGCTGTAGCTGGCTCCTCCGGGGTCCAGGCAGCAGCCA
CAGGGCAGAACTGACCATCTGGGCACCGCGTTCCAGCCACCAGCCCTGCTGTTAAGGCCACCCAGCTCACCAGG
GTCCACATGGTCTGCCTGCGTCCGACTCCGCGGTCCTTGGGCCCTGATGGTTCTACCTGCTGTGAGCTGCCCAAGACACT
TGGGAAGTATGGCTGCCCAATGCCCAACGCCACCTGCTCCCGATCACCTGCACTGCTCCCCAAGACACT
GTGTGTGACCTGATCCAGAGTAAGTGCCTCTCCAAGGAGAACG

11730-1

11730-2

Fig. 15C

38/101

11732.1contig

11732.2contig

11735-1-2

11740.2.contig

Fig. 15D

39/101 11765.2&64.2.contig

CGCCTCCACCATGTCCATCAGGGTGACCCAGAAGTCCTACAAGGTGTCCACCTCTGGCCCCCGGGCCTTCAGCA
GCCGCTCCTACACGAGTGGGCCCGGTTCCCGCATCAGCTCCTCGAGCTTCTCCCGAGTGGGCAGCAACTTT
CGCGGTGGCCTGGGCGGCGCGCTATGGTGGGGGCCAGCGCATCAGCGCAGCTCACCCGCAGTTACGGTCAACCAGAG
CCTGCTGAGCCCCCTTGTCCTGGAGGTGGACCCCAACATCCAGGCCGTGCGCACCCAGGAGAAGAAGGAGCAGATCA
AGACCCTCAACAACAAGTTTGCCTCCTTCATAGACAAGGTACGGTTCCTGGAGCAGCAGCAGAACAAGATGCTGGAG
ACCAAGTGGAGCCTCCTGCAGCAGCAGAAGACGGCTCGAAGCAACATGGACAACATGTTCGAGAGGCTACATCAA
CARCCTTAGGCGGCAGCTGGAGACTCTGGGCCAGGAGAAGATGAAGCTGGAGGCGGAGCTTGGCAACATGCAGG
GGCTGGTGGAGGACTTCAAGAACAAGTATGAGGATGAGATCAATAAGCGTACAGAGATGGAGAACCAATTTGTC
CTCATCAAGAAGGATGTGGATGAAGCTTACATGAACAAGGTAGAGCTGGAGTCCCAGATCTCGGACACATCTG
CGAGATCAACTTCCTCAGGCAGCTGTATGAAGAGGAGATCCCGGGAGCTCCCAGATCTCGGACACATCTG
TGGTGCTGTCCATGGACAACAGCCGCTCCCTGGACATGACAGCATCATTGCTCAGGGTCAAGGCACAGTACGAG
GATATTGCCAACCGCAGCCGGGCTGAGGCTGAGACATGACCAGGTCAAGTATGAGGAGCTCCAGAGCCTGGC
TGGGAAGCACGGGGATGACCTGCGGCGCCACAAAGACTGAGATCTCTGAGATGAACCCGGAACATCAGCCCGGCT
XCAGGCTGAGATTGAGGGCCTCAAAGGCCAGAXGCTTXCCTGGAXGXCCCGCAT
XCAGGCTGAGATTGAGGGCCTCAAAGGCCAGAXGGCTTXCCTGGAXGXCCCGCAT

11767.2.contig

CCCGGAGCCAACGAGCGGAAAATGGCAGACAATTTTTTCGCTCCATGATGCGTTATCTGGGTCTGGAAACCCCAAACCCTCAAGGATGGCCTGGCGCATGGGGGAACCAGCCTGCTGGGGCAGGGGCTACCCAGGGGCTTCCTATCCTGGGGCCTACCCCGGGCACCCCCAGGGGCCTACCCTGCAGCCACCTGGAGCACCTGCACCTGGAGCCTACCCAGGGCCCTACCCCATCCTGGAGCCTACCCAGGGCCCCTGGGGCCCTACCCCATCCTTCTGGACAGCCCAAGTGCCACCGGAGCCTACCCTGCACTGGCCCCTATGGCGCCCCTGCTGGGCCACTGATTGTCCCTTATAACCTGCCTTTGCCTGGGGAGTGATGCCTCGCATGCTGATAACAATTCTGGGCACGGTGAAGCCCAATGCAAACAGAACAACAGAATTCCTAGATTTCCAAAGAGGGAATGATGTTGCCTTCCACTTTAACCCACGCTTCAATGAGAACAACAGGAGAGTCATTGGTTGCAATACAAAGCTGGATAA

11768-1&2

40/101 11768-1&2-11735-1&2

11769.1.contig

11769.2.contig

AGCGCGGTCTTCCGGCGCGAGAAAGCTGAAGGTGATGTGGCCGCCCTCAACCGACGCATCCAGCTCGTTGAGGA
GGAGTTGGACAGGGCTCAGGAACGACTGGCCACGGCCCTGCAGAAGCTGGAGGAGGAGAAAAAGCTGCAGATG
AGAGTGAGAGAGAATGAAGGTGATAGAAAACCGGGCCATGAAGGATGAGGAGAAGATGGAGAATTCAGGAGATG
CAGCTCAAAGAGGCCAAGCACATTGCGGAAGAGGCTGACCGCAAATACGAGGAGGTAGCTCGTAAGCTGGTCAT
CCTGGAGGGTGAGCTGGAGAGAGGCGTGCGGAGGTGTCTGAACTAAAATGTGGTGACCTGGAAGAAG
AACTCAAGAATGTTACTAACAATCTGAAATCTCTGGAGGCTGCATCTGAAAAGTATTCTGAAAAGGAGGACAAA
TATGAAGAAGAAATTAAACTTCTGTCTGACAAACTGAAAGAGGCTGAGACCCGTGCTGAATTTGCAGAGAGAAAC
GGTTGCAAAACTGGAAAAGACAATTGATGACCTGGAAGAGAAACTTGCCCAGC

11770.1.contig

Fig. 15F

41/101 11770.2.contig

11773.1.contig

11778.1.contig

11778-2&30-2

Fig. 15G

42/101

11782.1.contig

ATCTACGTCATCAATCAGGCTGGAGACACCATGTTCAATCGAGCTAAGCTGCTCAATATTGGCTTTCAAGAGGC
CTTGAAGGACTATGATTACAACTGCTTTGTGTTCAGTGATGTGGACCTCATTCCGATGGACGACCGTAATGCCT
ACAGGTGTTTTTCGCAGCCACGGCACATTTCTGTTGCAATGGACAAGTTCGGGTTTAGCCTGCCATATGTTCAG
TATTTTGGAGGTGTCTCTGCTCTCAGTAAACAACAGTTTCTTGCCATCAATGGATTCCCTAATAATTATTGGGG
TTGGGGAGGAGAAGATGACGACATTTTTAACAGATTAGTTCATAAAGGCATGTCTATATCACGTCCAAATGCTG
TAGTAGGGAGGTGTCGAATGATCCGGCATTCAAGAGACAAGAAAAATGAGCCCAATCCTCAGAGGTTTGACCGG
ATCGCACATACAAAGGAAACGATGCGCTTCGATGGTTTGAACTCACTTACCTACAAGGTGTTGGATGTCAGAGA
TACCCGTTATATACCCAAATCAC

11782.2.contig

11783-1 & 2

11786.1.contig

GCTCTTCACACTTTTATTGTTAATTCTCTTCACATGGCAGATACAGAGCTGTCGTCTTGAAGACCACCACTGAC CAGGAAATGCCACTTTTACAAAATCATCCCCCCTTTTCATGATTGGAACAGTTTTCCTGACCGTCTGGGAGCGT TGAAGGGTGACCAGCACATTTGCACATGCAAAAAAAGGAGTGACCCCAAGGCCTCAACCACACTTCCCAGAGCTC ACCATGGGCTGCAGGTGACCTTGCCAGGTTTGGGGTTCGTGAGCTTTCCTTGCTGCTGCGGTGGGGAGGCCCTCA AGAACTGAGAGGCCGGGTATGCTTCATGAGTGTTAACATTTACGGGACAAAAAGCGCATCATTAGGATAAGGAA CAGCCACAGCACTTCATGCTTGTGAGGGTTAGCTGTAGGAGCGGGTGAAAGGATTCCAGTTTATGAAAATTTAA AGCAAACAACGGTTTTTAGCTGGGTGGGAAACAGGAAAACTGTGATGTCGGCCAATGACCACCATTTTTCTGCC CATGTGAAGGTCCCCATGAAACC

Fig. 15H

43/101

11786.2.contig

CAAGCGCTTGGCGTTTGGACCCAGTTCAGTGAGGTTCTTGGGTTTTGTGCCTTTGGGGATTTTGGTTTGACCCA GGGGTCAGCCTTAGGAAGGTCTTCAGGAGGAGGCCGAGTTCCCCTTCAGTACCACCCCTCTCTCCCCACTTTCC CTCTCCCGGCAACATCTCTGGGAATCAACAGCATATTGACACGTTGGAGCCGAGCCTGAACATGCCCCTCGGCC CCAGCACATGGAAAACCCCCTTCCTTGCCTAAGGTGTCTGAGTTTCTGGCTCTTGAGGCATTTCCAGACTTGAA ATTCTCATCAGTCCATTGCTCTTGAGTCTTTGCAGAGAAACCTCAGATCAGGTGCACCTGGGAGAAAGACTTTGT CCCCACTTACAGATCTATCTCCCCCTTGGGAAGGGCAGGGAATGGGGACGGTGTATGGAGGGGAAGGGATCTC CTGCGCCCTTCATTGCCACACTTGGTGGGACCATGAACATCTTTAGTGTCTGAGCTTCTCAAATTACTGCAATA

13691.182

13692.182

13693.2

Fig. 15I

44/101 13696.1-13744.1

13700.1

CAAGGGATATATGTTGAGGGTACRGRGTGACACTGAACAGATCACAAAGCACGAGAAACATTAGTTCTCTCCCT
CCCCAGCGTCTCCTTCGTCTCCCTGGTTTTCCGATGTCCACAGAGTGAGATTGTCCCTAAGTAACTGCATGATC
AGAGTGCTGKCTTTATAAGACTCTTCATTCAGCGTATCCAATTCAGCAATTGCTTCATCAAATGCCGTTTTTTGC
CAGGCTACAGGCCTTTTCAGGAGAGATTTAGAATCTCATAGTAAAAGACTGAGAAATTTAGTGCCAGACCAAGAC
GAATTGGGTGTGTAGGCTGCATTNCTTTCTTACTAATTTCAAATGCTTCCTGGTAAGCCTGCTGGGAGTTCGAC
ACAAGTGGTTTTGTTTGTTGCTCCAGATGCCACTTCAGAAAGATACCTAAAATAATCTCCTTTCATTTTCAAAGT
AGAACAC

13700.2

13701.1

45/101

13701.2

13702.2

AGCTGGCGCTAGGGCTCGGTTGTGAAATACAGCGTRGTCAGCCCTTGCGCTCAGTGTAGAAACCCACGCCTGTA AGGTCGGTCTTCGTCCATCTGCTTTTTTCTGAAATACACTAAGAGCAGCCACAAAACTGTAACCTCAAGGAAAC CATAAAGCTTGGAGTGCCTTAATTTTTAACCAGTTTCCAATAAAACGGTTTACTACCT

13704.2-13740.2

GGAGATGAAGATGAGGAAGCTGAGTCAGCTACGGGCARGCGGGCAGCTGAAGATGATGAGGATGACGATGTCGA TACCAAGAAGCAGAAGACCGACGACGATGACTAGACAGCAAAAAAGGAAAAGTTAAA

13706.1

GATGAAAATTAAATACTTAAATTAATCAAAAGGCACTACGATACCACCTAAAACCTACTGCCTCAGTGGCAGTA KGCTAAKGAAGATCAAGCTACAGSACATYATCTAATATGAATGTTAGCAATTACATAKCARGAAGCATGTTTGC TTTCCAGAAGACTATGGNACAATGGTCATTWGGGCCCAAGAGGATATTTGGCCNGGAAAGGATCAAGATN AANGTAAAG

13706.2

Fig. 15K

46/101

13707.3

13710.2

13710-1

TGAGATTTATTGCATTTCATGCAGCTTGAAGTCCATGCAAAGGRGACTAGCACAGTTTTTAATGCATTTAAAAA ATAAAAGGGAGGTGGGCAGCAAACACACAAAGTCCTAGTTTCCTGGGTCCCTGGGAGAAAAGAGTGTGGCAATG AATCCACCCACTCTCCACAGGGAATAAATCTGTCTCTTTAAATGCAAAGAATGTTTCCATGGCCTCTGGATGCAA ATACACAGAGCTCTGGGGTCAGAGCAAGGGATGGGGAGAGACACACATTCAC CTAATTCCATCTGAGGGCAAGAACAACGTGGCAAGTCTTGGGGGTAGCAGCTGTT

13711.1

Fig. 15L

47/101

13711.2

13713.1&2

TCACTTTATTTTCTTGTATAAAAACCCTATGTTGTAGCCACAGCTGGAGCCTGAGTCCGCTGCACGGAGACTC
TGGTGTGGGTCTTGACGAGGTCGTCAGTGAACTCCTGATAGGGAGACTTTGGTGAATACAGTCTCCTTCCAGAGG
TCGGGGGTCAGGTAGCTGTAGGTCTTAGAAATGGCATCAAAGGTGGCCTTGGCGAAGTTGCCCAGGGTGGCAGT
GCAGCCCCGGGCTGAGGTGTAGCAGTCATCGATACCAGCCATCATGAG

13715.4

13717.182

TGAATGGGAGGAGCTGACCCAGGAAATGGAGCTTGNGGAGACCAGGCCTGCAGGGGATGGAACCTTCCAGAAG
TGGGCATCTGTGGTGCCTCTTGGGAAGGAGCAGAAGTACACATGCCATGTGGAACATGAGGGGCTGCCTGA
GCCCCTCACCCTGAGATGGGGCAAGGAGGAGCCTCCTTCATCCACCAAGACTAACACAGTAATCATTGCTGTTC
CGGTTGTCCTTGGAGCTGTGGTCATCCTTGGAGCTGTGATGGCTTTTTGTGATGAAGAGGAGGAGAAACACAGGT
GGAAAAGGAGGGGACTATGCTCTGGCTCCAGGCTCCCAGAGCTCTGATATGTCTCTCCCAGATTGTAAAGTGTG
AAGACAGCTGCCTGGTGTGGACTTGGTGACAGACAATGTCTTCACACATCTCCTGTGACATCCAGAGACCTCAG
TTCTCTTTAGTCAAGTGTCTGATGTTCCCTGTGAGTCTGCGGGCTCAAAGTGAAGAACTGTGGAGCCCAGTCCA
CCCCTGCACACCAGGACCCTATCCCTGCACTGCCCTGTGTTCCCTTCCACAGCCAACCTTGCTGCTCCAGCCAA
ACATTGGTGGACATCTGCAGCCTGTCAGCTCCATGCTACCTTCCACACTCCTCACTTCCACACTGAGAAT
AATAATTTGAATGTGGGTGGCTCACAACCATCTGTAATGGGATCTAATACCCTTTCTGCAGTGTCTGAAGACASCT
ACAGTGTACTTACATATAATAATAATAAATAAA

Fig. 15M

48/101 13719.182

13721.1

13721.2

13723.1

CATGGGTTTCACCAGGTTGGCCAGGCTGCTCTTGAACTSCTGACCTCAGGTGATCCACCCGCCTCGGCCTCCCA
AAGTGCTGGGATTACAGGCGTGAGCCACCACGCCCGGCCCCCAAAGCTGTTTCTTTTTGTCTTTAGCGTAAAGCT
CTCCTGCCATGCAGTATCTACATAACTGACGTGACTGCCAGCAAGCTCAGTCACTCCGTGGTCTTTTTCTCTTT
CCAGTTCTTCTCTCTCTCTCTAGGTTCTGCCTCAGTGAAAGCTGCAGGTCCCCAGTTAAGTGATCAGGTGAGGG
TTCTTTGAACCTGGTTCTATCAGTCGAATTAATCCTTCATGATGG

49/101

13723.2

13725.1

13725.2

13726.1&2

50/101

13727.1

13727.2

ACCTAGACAGAAGGTGGGTGAGGGAGGACTGGTAGGAGGCTGAGGCAATTCCTTGGTAGTTTGTCCTGAAACCC
TACTGGAGAAGTCAGCATGAGGCACCTACTGAGAGAAGTGCCCAGAAACTGCTGACTGCATCTGTTAAGAGTTA
ACAGTAAAGAGGTAGAAGTGTTTTCTGAATCAGAGTGGAAGCGTCTCAAGGGTCCCACAGTGGAGGTCCCTGA
GCTACCTCCCTTCCGTGAGTGGGAAGAGTGAAGCCCATGAAGAACTGAGATGAAGCAAGGATGGGGTTCCTGGG
CTCCAGGCAAGGGCTGTGCTCTCTGCAGCAGGAGGCCCCACGAGTCAGAAGAAAAAGAACTAATCATTTGTTGCA
AGAAACCTTGCCCGGATACTAGCGGAAAACTGGAGGCGGNGGTGGGGGCACAGGAAAGTGGAAGTGATTTGATG
GAGAGCAGAGAAGCCTATGCACAGTGGCCGAGTCCACTTGTAAAGTG

13728.182

13731.1&2

51/101

13734.182

13736.2

13744.2-13696.2

13746.1&2-13720.1&2

52/101 14347 1

14347.2

14348.2&14350.1&2

14349.1&2

Fig. 15R

53/101 14352.1&2

14353.1

14353.2

17182.1&2

54/101 17183.2

GGTTCACAGCACTGCTGCTTGTGTTGCCGGCCAGGAATTCCAGGCTCACAAGGCTATCTTAGCAGCTCGTTC
TCCGGTTTTTAGTGCCATGTTTGAACATGAAATGGAGGAGAGCAAAAAGAATCGAGTTGAAATCAATGATGTGG
AGCCTGAAGTTTTTAAGGAAATGATGTGCTTCATTTACACGGGGAAGGCTCCAAACCTCGACAAAATGGCTGAT
GATTTGCTGGCAGCTGCTGACAAGTATGCCCTGGAGCGCTTAAAGGTCATGTGTGAGGATGCCCTCTGCAGTAA
CCTGTCCGTGGAGAAACGCTGCAGAAATTCTCATCCTGGCCGACCTCCACAGTGCAGATCAGTTGAAAACTCAGG
CAGTGGATTTCATCAACTATCATGCTTCGGATGTCTTGGAGACCTCTTGGG

17186.1&2

17187.182

17191.1889.1

55/101 17192.1&2

17193

56/101

16443.1.edit

16443.2.edit

16444.2.edit

AGCGTGGTTNCGGCCGAGGTCCCAACCAAGGCTGCANCCTGGATGCCATCAAAGTCTTCTGCAACATGGAGACT GGTGAGACCTGCGTGTACCCCACTCAGCCCAGTGTGGCCCAGAAGAACTGGTACATCAGCAAGAACCCCAAGGA CAAGAGGCATGTCTGGTTCGGCGAGAGCATGACCGATGGATTCCAGTTCGAGTATGGCGGCCAGGGCTCCGACC CTGCCGATGTGGACCTGCCCGGGCGGNCGCTCGA

16445.1.edit

AGCGTGGTCGCGGCCGAGGTCAAGAACCCCGCCCGCACCTGCCGTGACCTCAAGATGTGCCACTCTGACTGGAA GAGTGGAGAGTACTGGATTGACCCCAACCAAGGCTGCAACCTGGATGCCATCAAAGTCTTCTGCAACATGGAGA CTGGTGAGACCTGCGTGTACCCCACTCAGCCCAGTGTGGCCCAGAAGAACTGGTACATCAGCAAGAACCCCAAG GACAAGAGGCATGTCTGGTTCGGCGAGAGCATGACCGATGGATTCCAGTTCGAGTATGGCGGCCAGGGCTCCGA CCCTGCCGATGTGGACCTGCCCGGGCGGCCGCTCGA

Fig. 15V

57/101

16445.2.edit

16446.1.edit

TCGAGCGCCCCCGGCAGGTCCTCCTCAGAGCGGTAGCTGTTCTTATTGCCCCGGCAGCCTCCATAGATNAA GTTATTGCANGAGTTCCTCCACCGTCAAAGTACCAGCGTGGGAAGGATGCACGGCAAGGCCCAGTGACTGCGT TGGCGGTGCAGTATTCTTCATAGTTGAACATATCGCTGGAGTGGACTTCAGAATCCTGCCTTCTGGGAGCACTT GGGACAGAGGAATCCGCTGCATTCCTGCTGGTGGACCTCGGCCGCCGACCACGCT

16446.2.edit

AGCGTGGTCGCGGCCGAGGTCCACCAGCAGGAATGCAGCGGATTCCTCTGTCCCAAGTGCTCCCAGAAGGCAGG ATTCTGAAGACCACTCCAGCGATATGTTCAACTATGAAGAATACTGCACCGCCAACGCAGTCACTGGGCCTTGC CGTGCATCCTTCCCACGCTGGTACTTTGACGTGGAGAGGAACTCCTGCAATAACTTCATCTATGGAGGCTGCCG GGGCAATAAGAACAGCTACCGCTCTGAGGAGGACCTGCCCGGGCGGCCGCTCGA

16447.1.edit

Fig. 15W

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16449.1.edit

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16450.2.edit

Fig. 15X

59/101 16451.1.edit

16451.2.edit

TCGAGCGGCCGCCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCAATCTTGTAGTTCACACCAT TGTCATGGCACCACTCTCAAAGCCCACTCCCAAAGCCTAAGCACTGGCACAACAGTTTA AAGCCTGATTCAGACATTCCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA GTCATCCGTAGGTTGATCAAGCCTTCGNTGACAGAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGCC TCTGCTGGTCTTCAGTGCCTCCACTATGATGTTGTAGGTGGTACCTCTGGTGAGGACCTCGGCCGCACCACG CT

16452.1.edit

16452.2.edit

Fig. 15Y

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16453.2.edit

16454.1.edit

AGCGTGGNTGCGGACGCCCACAAAGCCATTGTATGTAGTTTTANTTCAGCTGCAAANAATACCNCCAGCAT CCACCTTACTAACCAGCATATGCAGACA

16454.2.edit

TCGAGCGGTCGCCCGGGCAGGTCTGGGCGGATAGCACCGGGCATATTTTGGAATGGATGAGGTCTGGCACCCTG
AGCAGCCCAGCGAGGACTTGGTCTTAGTTGAGCAATTTGGCTAGGAGGATAGTATGCAGCACGGTTCTGAGTCT
GTGGGATAGCTGCCATGAAGNAACCTGAAGGAGGCGCTGGCTGGTANGGGTTGATTACAGGGCTGGGAACAGCT
CGTACACTTGCCATTCTCTGCATATACTGGNTAGTGAGGCGAGCCTGGCGCTCTTCTTTGCGCTGAGCTAAAGC
TACATACAATGGCTTTGNGGACCTCGGCCGCGACCACGCTT

Fig. 15Z

61/101 16455.1.edit

TCGAGCGGCCGCCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCAATCTTGTAGTTCACACCAT
TGTCATGACACCATCTGAAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA
AAGCCTGATTCAGACATTCGTTCCCACTCTCCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA
GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGC
CTCTGCTGGTCTTTCAAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTCGGCCGCCACCA
CGCT

16455.2.edit

16456.1.edit

AGCGTGGTCGCGGCCGAGGTCTGCTTNCTGCTCANGTGATTATCCTGAACCATCCAGGCCAAATAAGCGCCGGCTATGCCCCTGNATTGGATTGCCACACGGCTCACATTGCATGCAAGTTTGCTGAGCTGAAGGAAAAGATTGATC

16456.2.edit

Fig. 15AA

62/101 16459.1.edit

16459.2.edit

16460.1.edit

TCGAGCGCCCCCGGGCAGGTCCATTTTCTCCCTGACGGNCCCACTTCTCTCCAATCTTGTAGTTCACACCAT
TGTCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCCAAAGCCTAAGCACTGGCACAACAGTTTA
AAGCCTGATTCAGACATTCCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA
GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACGGTAACAACCTCNTCCCCGAACCTTATGC
CTCTGCTGGGCTTTCAGNGCCTCCACTATGATGNTGTAGGGGGGCACCTCTGGNGANGACCTCGGCCGCACCA
CGCT

16460.2.edit

Fig. 15BB

63/101

16461.1.edit

16461.2.edit

16463.1.edit

AGCGTGGNNGCGGCCGAGGTATAAATATCCAGNCCATATCCTCCCTCCACACGCTGANAGATGAAGCTGTNCAA AGATCTCAGGGTGGANAAAACCAT

16463.2.edit

Fig. 15CC

64/101

16464.1.edit

CGAGCGGCCGCCCGCCCTGNTGTCCCANANAACCATCAAGCCAGATGTCAGAAGCTACACCATCA CAGGTTTACAACCAGGCACGCTACAAGANCTACCTGCACCACCCTTGAATGACAATGCTCGGAGCTCCCCTGTG GTCATCGACGCCTCCACTGCCATTGATGCACCATCCAACCTGCGTTTCCTGGCCACCACCCCAATTCCTTGCT GGTATCATGGCAGCCGCCACGTGCCAGGATTACCGGTACATCATCNAGTATGANAAGCCTGGGCCTCCTCCCAG AGAAGNGGTCCCTCGGCCCCCGCCTGNTGTCCCANAGGNTACTATTACTGNGCCNGCAACCGGCAACCGATATC NATTTTGNCATTGGCCTTCAACAATAATTA

16464.2.edit

AGCGTGGTTCGCGGCCGANGTCCTGTCAGAGTGGCACTGGTAGAAGTTCCAGGAACCCTGAACTGTAAGGGTTC
TTCATCAGNGCCAACAGGATGACATGAAATGATGTACTCAGAAGTGTCCTGGAATGGGGCCCATGAGATGGTTG
TCTGAGAGAGAGCTTCTTGNCCTGTCTTTTTCCTTCCAATCAGGGGCTCGCTCTTCTGATTATTCTTCAGGGCA
ATGACATAAATTGTATATTCGGGTCCCGGNTCCAGGCCAGTAATAGTANCCTCTGTGACACCAGGGCGGNGCCG
AGGGACCACTTCTCTGGGAGGAGACCCAGGCTTCTCATACTTGATGATGATGAACCGGTAATCCTGGCACGTGGCG
GCTGCCATGATACCAGCAAGGAAATTGGGGTGTGGCCAGGAAACGCAGGTTGGATGGNGCATCAATGGCAGT
GGAGGCCGTCGATGACCACAGGGGGAGCTCCGACATTGTCATTCAAGGTG

16465.1.edit

AGCGTGGNCGCGGCCGAGGTGCAGCGCGGGCTGTGCCACCTTCTGCTCTCTGCCCAACGATAAGGAGGGTNCCTGCCCCAGGAGAACATTAACTNTCCCCAGCTCGGCCTCTGCCGG

16465.2.edit

TCGAGCGGCCGCCCGGGCAGGTTTTTTTTTGCTGAAAGTGGNTACTTTATTGGNTGGAAAGGGAGAAGCTGTGG
TCAGCCCAAGAGGGAATACAGAGNCCCGAAAAAGGGGAGGGCAGGTGGGCTGGAACCAGACCAGGACCAGGCCAGGCA
GAAACTTTCTCTCCTCACTGCTCAGCCTGGTGGTGGTGGCTGGAGCTCANAAATTGGGAGTGACACAGGACACCTTC
CCACAGCCATTGCGGCGGCATTTCATCTGGCCAGGACACTGGCTGTCCACCTGGCACTGGTCCCGACAGAAGCC
CGAGCTGGGGAAAGTTAATGTTCACCTGGGGGCAGGAACCCTCCTTATCATTGNGCAGAGAGCAGAAGGTGGCA
CAGCCCGCGCTGCACCTCGGCCGCGACCACGCT

16466.2.edit

TCGAGCGCCCCGGGCAGGTCCACCATAAGTCCTGATACAACCACGGATGAGCTGTCAGGAGCAAGGTTGAT
TTCTTTCATTGGTCCGGNCTTCTCCTTGGGGGGNCACCCGCACTCGATATCCAGTGAGCTGAACATTGGGTGGCG
TCCACTGGGCGCTCAGGCT

16467.2.edit

TCGAGCGGTTCGCCCGGGCAGGTCCACCACACCCAATTCCTTGCTGGTATCATGGCAGCCGCCCACGTGCCAGGA
TTACCGGCTACATCAAGTATGAGAAGCCTGGGTCTCCCCCAGAGAAGCGGTCCCTCGGCCCCTGGT
GTCACAGAGGCTACTATTACTGGCCTGGAACCGGGAACCGAATATACAATTTATGTCATTGNCCTGAAGAATAA
TCANNAANAGCGANCCCCTGATTGGAAGGA

Fig. 15DD

65/101 01_16469.edit

02 16469.edit

03 16470.edit

04_16470.edit

TCGAGCGCCCCCGGGCAGGTCCTGTCAGAGTGGCACTGGTAGAAGTTCCAGGAACCCTGAACTGTAAGGGTT CTTCATCAGTGCCAACAGGATGACATGAAATGATGTACTCAGAAGTGTCCTGGAATGGGGCCCATGAGATGGTT GTCTGAGAGAGAGGCTTCTTGTCCTACATTCGGCGGGTATGGTCTTGGCCTATGCCTTATGGGGGTGGCCGTTGT GGGCGGTGTGGTCCGCCTAAAACCATGTTCCTCAAAGATCATTTGTTGCCCAACACTGGGTTGCTGACCAGAAG TGCCAGGAAGCTGAATACCATTTCACCTCGGCCGCGACCACGCTA

05 16471.edit

TCGAGCGCCCCGGGCAGGTCTCCCTTCTTGCGGCCCAGGGGCAGCGCATAGTGGGACTCGTACCACTGTCG
GTACGGTGTGCTGTCGATGAGCACGATGCAATTCTTCACCAGGGTCTTGGTACGAACCAGCTCGTTATTAGATG
CATTGTAGACAACATCGATGATCCTTGTTTTACGAGTACAACACTCTGAGCCCCAGGAGAAATTCCCCACGTCC
AACCTCAGGGCACGGTATTTCTTGTTACCTCCCCGCACACGGACTGTGTGGATGCGGCGGGGGCCAAGCTGACT
CCTGAGGAAGAAGAAGAATTTAAACAAAAAACGATCTAAAAAAATTCAGAAGAAATATGATGAAAGGAAAAAAGAA
TGCCAAAATCAGCAGTCTCCTGGAGGAGCAGTTCCAGCAGGGCAAGCTTCTTGCGTGCATCGCTTCAAGGCCGG
GACAGTGTGACCGAGCAGATGGCTATGTGCTAGAGGGCCAAAGAAGTGGAGTTCTATCTTAAGAAAAATCAGGGCC
CAGAATGGTGNGTCTTCAACTAATCCAAAGGGGAGTTTCAGACCAGTGCAATCAGCAAAAACATTGATACTGNT
GGCCAAATTTATTGGTGCAGGGCTTGCACANTANGANNGGCTGGGTCTTGGGGCTTGGATTGGNACAAGCTTTG
GCAGCCTTTTCTTTGGTTTTGCCAAAAACCTTTTGNTGAAGANGANACCTNGGGCGGACCCCTTAACCGATTCC
ACNCCNGGNGGCGTTCTANGGNCCCNCTTG

Fig. 15EE

66/101 06 16471.edit

AGCGTGGTCGCGGCCGAGGTCTGCTGCTTCAGCGAAGGGTTTCTGGCATAACCAATGATAAGGCTGCCAAAGAC
TGTTCCAATACCAGCACCAGAACCAGCCACTCCTACTGTTGCAGCACCTGCACCAATAAATTTGGCAGCAGTAT
CAATGTCTCTGCTGATTGCACTGGTCTGAAACTCCCTTTGGATTAGCTGAGACACACCATTCTGGGCCCTGATT
TTCCTAAGATAGAACTCCAACTCTTTGCCCTCTAGCACATAGCCATCTGCTCGGTCACACTGTCCCGGCCTTGA
AGCGATGCACGCAAGAAGCTTGCCCTGCTGGAACTGCTCCTCCAGGAGACTGCTGATTTTTGGCATTCTTTTTCC
TTTCATCATATTTCTTCTGAATTTTTTTTAGATCGTTTTTTTGTTTAAAATCTCTTCTTCCTCAGGAGTCAGCTTG
GCCCCCGCCGCATCCACACAGTCCGTGTGCGGGGAGGTAACAAGAAATACCGTGCCCTGAGGTTGGACGTGGGG
AATTTCTCCTGGGGCTCAGAGTGGTGTACTCGTAAAACAAGGATCATCGATGGTGNCTACAATGCATCTAATAA
CGAGCTGGGTCGGACCCAAAGAACCTGGNGAANAAATGGATCGNCTCATCGACAGGACACCGTACCCGACAGGG
GNACGANTCCCACTATGCGCTTGCCCCTGGGCCGCAANAAAGGAAAACTGCCCGGGCGGCCNTCGAAAGCCCAA
TTNTGGAAAAAATCCATCACACTGGGNGGCCNGTCGAGCATGCATNTANAGGGGCCCCATTCCCCCTNANN

07 16472.edit

TCGAGCGGCCGCCCGGGCAGGTCCCCAACCAAGGCTGCAACCTGGATGCCATCAAAGTCTTCTGCAACATGGAG ACTGGTGAGACCTGCGTGTACCCCACTCAGCCCAGTGTGGCCCAGAAGAACTGGTACATCAGCAAGAACCCCAA GGACAAGAGGCATGTCTGGTTCGGCGAGAGCATGACCGATGGATTCCAGTTCGAGTATGGCGGCCAGGGCTCCG ACCCTGCCGATGTGGACCTCGGCCGCCACCGCT

08 16472.edit

AGCGTGGTCGCGGCCGAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATCGG TCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCACA CTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTGCA GCCTTGGTTGGGGACCTGCCCGGGCGGCCGCTCGA

09 16473.edit

Fig. 15FF

67/101 11 16474.edit

12 16474.edit

13 16475.edit

TCGAGCGCCCCCGGGCAGGTCTGGTCCAGGATAGCCTGCGAGTCCTCCTACTGCTACTCCAGACTTGACATC
ATATGAATCATACTGGGGAGAATAGTTCTGAGGACCAGTAGGGCATGATTCACAGATTCCAGGGGGGCCAGGAG
AACCAGGGGACCCTGGTTGTCCTGGAATACCAGGGTCACCATTTCTCCCAGGAATACCAGGAGGCCTGGATCT
CCCTTGGGGCCTTGAGGTCCTTGACCATTAGGAGGGCGAGTAGGAGCAGTTGGAGGCTGTGGGCAAACTGCACA
ACATTCTCCAAATGGAATTTCTGGGTTGGGGCAGTCTAATTCTTGATCCGTCACATATTATGTCATCGCAGAGA
ACGGATCCTGAGTCACAGACACATATTTTGGCATGGTTCTGGCTTCCAGACATCTCTATCCGNCATAGGACTGAC
CAAGATGGGAACATCCTCCTTCAACAAGCTTNCTGTTGTGCCAAAAATAATAGTGGGATGAAGCAGACCGAGAA
GTANCCAGCTCCCCTTTTTTGCACAAAGCNTCATCATGTCTAAATATCAGACATGAGACTTCTTTGGGCAAAAAAA
GGAGAAAAAGAAAAAGCAGTTCAAAGTANCCNCCATCAAGTTGGTTCCTTGCCCNTTCAGCACCCGGGCCCCGT
TATAAAACACCCTNGGGCCGGACCCCCCCTT

Fig. 15GG

68/101 14 16475.edit

AGCGTGGTCGCGGCCGAGGTGTTTTATGACGGGCCCGGTGCTGAAGGGCAGGAACAACTTGATGGTGCTACTT
TGAACTGCTTTTCTCTTTTTCTCCTTTTTGCACAAGAGTCTCATGTCTGATATTTTAGACATGATGAGGCTTTGTGCA
AAAGGGGAGCTGGCTACTTCTCGCTCTGCTTCATCCCACTATTATTTTTGGCACAACAGGAAGCTGTTGAAGGAG
GATGTTCCCATCTTGGTCAGTCCTATGCGGATAGAGATGTCTGGAAGCCAGAACCATGCCAAATATGTGTCTGT
GACTCAGGATCCGTTCTCTGCGATGACATAATATGTGACGATCAAGAATTAGACTGCCCCAACCCAGAAATTCC
ATTTGGAGAATGTTGTGCAGTTTGCCCACAGCCTCCAACTGCTCCTACTCGCCCTCCTAATGGTCAAGGACCTC
AAGGCCCCAAGGGAGATCCAGGCCCTCCTGGTATTCCTGGGAGAAATGGTGACCCTGGTATTCCAGGACAACCA
GGGTCCCCTGGTTCTCCTGGCCCCCCTGGAATCNGGNGAATCATGCCCTACTGGTCCTCAAACTATTCTCCCAN
ATGATTCATATGATGTCAAGTCTGGGATAGCNAGTANGGANGGACTCGCAGGCTATTCTGGACCANACCTGCCC
GGGGGGGCGTTCGAAAGCCCGAATCTGCANANNTNCNTTCACACTGGCGGCCGTCGAGCTGCTTTAAAAAGGGCCA
TTCCNCCTTTAGNGNGGGGGGANTACAATTACTNGGCGGCGTTTTTANANCGCGNGNCTGGGAAAT

15 16476.edit

AGCGTGGTCGCGGCCGAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATCGC
TCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCACA
CTGGGCTGAGTGGGGTACACCGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTGCA
GCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGGTCACGGCAGGTGC
GGGCGGGGTTCTTGCGGCTCCCCTCTGGGCTCCGGATGTTCTCCATCTGCTGGCTCAGGCTCTTGAGGGTGGTC
TCCACCTCGAGGTCACGGAACCACATTGGCATCATCAGCCCGGTAGTAGCCGCCACCATCGTGAGCCTT
CTCTTGANGTGGCTGGGGCAGGAACTGAAGTCGAAACCAGCGCTGGGAGGACCAGAGACCAAAAGGTCCAGC
AAGGGCCCGGGGGGGACCAACAGGACCAGCATCACCAAGTGCGACCCGCGAGAACCTGCCCGGCCGNCCGCTCC
AA

16 16476.edit

Fig. 15HH

69/101 17_16477.edit

18 16477.edit

AGCGTGGTTNGCGGCCGAGGTCTGGGCCAGGGGCACCAACACGTCCTCTCTCACCAGGAAGCCCACGGGCTCCTGTTTGACCTGGAGTTCCATTTTCACCAGGGGCACCAGGTTCACCCTTCACACCAGGAGCACCGGGCTGTCCCTTCAATCCATNCAGACCATTGTGNCCCCTAATGCCTTTGAAGCCAGGAAGTCCAGGAGTTCCAGGGAAACCACCGAGCACCCTGTGGTCCAACAACTCCTCTCTCACCAGGTCGTCCGGGTTTTCCAGGGTGACCATCTTCACCAGCCTTGCCAGGAGGACCAGCAGCAGCAGCAGCAGACCAGCCTTACCAACCTGCCCGGGCGGCCGCTCGA

21 16479.edit

TCGAGCGCCCCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCAATCTTGTAGTTCACACCAT TGTCATGGCACCACTCTCAAAGCCCACTCTCCAAAGCCCAACCACTCTCAAAGCCCTAAGCACTGGCACAACAGTTTA AAGCCTGATTCAGACATTCCCCACTCATCTCCCAACGGCATAATGGGAAACCTGTGTAGGGGTCAAAGCACGA GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGCC TCTGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTCGGCCGCGACCACG CT

22 16479.edit

Fig. 15II

70/101 24 16480.edit

TCGAGCGNNCGCCCGGGCAGGTCCAGTAGTGCCTTCGGGACTGGGTTCACCCCCAGGTCTGCGGCAGTTGTCAC
AGCGCCAGCCCCGCTGGCCTCCAAAGCATGTGCAGGAGCAAATGGCACCGAGATATTCCTTCTGCCACTGTTCT
CCTACGTGGTATGTCTTCCCATCATCGTAACACGTTGCCTCATGAGGGTCACACTTGAATTCTCCTTTTCCGTT
CCCAAGACATGTGCAGCTCATTTGGCTGGCTCTATAGTTTGGGGAAAGTTTGTTGAAACTGTGCCACTGACCTT
TACTTCCTCCTTCTCTACTGGAGCTTTCGTACCTTCCACTTCTGCTGTTGGTAAAATGGTGGATCTTCTATCAA
TTTCATTGACAGTACCCACTTCTCCCCAAACATCCAGGGAAAATAGTGATTTCAGTGGTGACTTTAAAAGAATA
ATGGGGCAGAAATAAGGGGCTTTTCCACAGGTTTTCCTTTGGAGGAAGATTTCAGTGGTGACTTTAAAAGAATA
CTCAACAGTGTCTTCATCCCCATAGCAAAAGAAGAAACNGTAAATGATGGAANGCTTCTGGAGATGCCNNCATT
TAAGGGACNCCCAGAACTTCACCATCTACAGGACCTACTTCAGTTTACANNAAGNCACATANTCTGACTCANAA
AGGACCCAAGTAGCNCCATGGNCAGCACTTTNAGCCTTTCCCCTGGGGAAAANNTTACNTTCTTAAANCCTNGG
CCNNGACCCCCTTAAGNCCAAATTNTGGAAAAANTTCCNTNCNNCTGGGGGGCNGTTCNACATGCNTTTNAAGGG
CCCAATTNCCCCNT

25 16481.edit

26 16481.edit

27 16482.edit

TCGAGCGCCCCGGGCAGGTTGAATGGCTCCTCGCTGACCACCCCGGTGCTGGTGGTGGTACAGAGCTCCG ATGGGTGAAACCATTGACATAGAGACTGTCCCTGTCCAGGGTGTAGGGGCCCAGCTCAGTGATGCCGTGGGTCA GCTGGCTCAGCTTCCAGTACAGCCGCTCTCTGTCCAGTCCAGGCCTTTTGGGGTCAGGACGATGGGTGCAGACA GCATCCACTCTGGTGGCTGCCCCATCCTTCTCAGGCCTGAGCAAGGTCAGTCTGCAACCAGAGTACAGAGAGCT GACACTGGTGTTCTTGAACAAGGGCATAAGCAGACCCTGAAGGACACCTCGGCCGCCGACCACGCT

Fig. 15JJ

71/101 28 16482.edit

29 16483.edit

31 16484.edit

37 16487.edit

AGCGTGGTCGCGGCCGAGGTCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCT CCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGAGA GTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTC AGTCTTCCTCTTCCCCCGCATCCCCCTTCCAAACCTGCCCGGGCCGCCCCCC

Fig. 15KK

72/101 38 16487.edit

CGAGCGGCCGCCCGGGCAGGTTTGGAAGGGGGATGCGGGGGAAGAGAGACTGACGGTCCCCCCAGGAGTTCA GGTGCTGGGCACGGTGGGCATGTTGTGAGTTTTGTCACAAGATTTGGGCTCAACTCTCTTGTCCACCTTGGTGTT GCTGGGCTTGTGATCTACGTTGCAGGTGTAGGTCTGGGTGCCGAAGTTGCTGGAGGGCACGGTCACCACGCTGC TGAGGGAGTAGAGTCCTGAGGACTGTAGGACAGACCTCGGCCGCGACCACGCT

39 16488.edit

NGGNNGGTCCGGNCNGNCAGGACCACTCNTCTTCGAAATA

41 16489.edit

42 16489.edit

45 16491.edit

TCGAGCGGCCGCCCGGGCAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATC
GGTCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCA
CACTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTG
CAGCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGT
GCGGGCGGGGTTCTTGACCTCGGCCGCGCCACCACGCT

Fig. 15LL

73/101 46 16491.edit

47_16492.edit

AGCGTGGTCGCGGCCGAGGTCTGGGATGCTCCTGCTGTCACAGTGAGATATTACAGGATCACTTACGGAGAAAC
AGGAGGAAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGGAGACAGTCTACAGCTACCATCAGCGGCCTTAAAC
CTGGAGTTGATTATACCATCACTGTGTATGCTGTCACTGGCCGTGGAGACAGCCCCGCAAGCAGCAAGCCAATT
TCCATTAATTACCGAACAGAAATTGACAAACCATCCCAGATGCAAGTGACCGATGTTCAGGACAACAGCATTAG
TGTCAAGTGGCTGCCTTCAAGTTCCCCTGTTACTGGTTACAGAGTAACCACCACTCCCAAAAAATGGACCAGGAC
CAACAAAAACTAAAACTGCAGGTCCAGATCAAACAGAAATGACTATTGAAGGCTTGCAGCCCACAGTGGAGTAT
GTGGTTAAGTGTCTATGCTCAGAATCCAAGCGGAGAGAAGTCAGCCTCTGGTTCAGACTGNAAGTAACCAACAT
TGATCGCCTAAAGGACTGGCATTCACTGATGNGGATGCCGATTCCATCAAAATTGNTTGGGAAAAACCCACAGGG
GCAAGTTTNCANGTCNAGGNGGACCTACTCGAGCCCTGAGGATGGAATCCTTGACTNTTCCTTNNCCTGATGGG
GAAAAAAAAACCTTNAAAACTTGAAGGACCTGCCCGGGCGGCCGTNCAAAACCCAATTCCACCCCCTTGGGGGCG
TTCTATGGGNCCCACTCGGACCAAACTTGGGGTAAN

48 16492.edit

Fig. 15MM

74/101 49 16493.edit

55 16496.edit

56_16496.edit

TCGAGCGGCCGCCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCCAATCTTGTAGTTCACACCAT
TGTCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA
AAGCCTGATTCAGACATTCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA
GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGCC
TCTGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTCGGCCGCCACCACG
CT

59 16498.edit

TCGAGCGCCCCCGGGCAGGTCCACCATAAGTCCTGATACAACCACGGATGAGCTGTCAGGAGCAAGGTTGAT
TTCTTTCATTGGTCCGGTCTTCTCCTTGGGGGTCACCCCGCACTCGATATCCAGTGAGCTGAACATTGGGTGGTG
TCCACTGGGCGCTCAGGCTTGTGGGTGTGACCTGAGTGAACTTCAGGTCAGTTGGTGCAGGAATAGTGGTTACT
GCAGTCTGAACCAGAGGCTGACTCTCTCCGCTTGGATTCTGAGCATAGACACTAACCACATACTCCACTGTGGG
CTGCAAGCCTTCAATAGTCATTTCTGTTTGATCTGGACCTGCAGTTTTAGTTTTTGTTGGTCCTGGTCCATTTT
TGGGAGTGGTGGTTACTCTGTAACCAGTAACAGGGGAACTTGAAGGCAGCCACTTGACACTAATGCTGTTGTCC
TGAACATCGGTCACTTGCATCTGGGATGGTTTGNCAATTTCTGTTCGGTAATTAATGGAAATTGGCTTGCTGCT
TGCGGGGCTGTCTCCACGGCCAGTGACAGCATACACAGNGATGGNATNATCAACTCCAAGTTTAAGGCCCTGAT
GGTAACTTTAAACTTGCTCCCAGCCAGNGAACTTCCGGACAGGGTATTTCTTCTGTTTTCCGAAAGNGANCCT
GGAATNNTCTCCTTGGANCAGAAGGANCNTCCAAAACTTGGGCCGGAACCCCTT

Fig. 15NN

75/101 60 16473.edit

60 16498.edit

61 16499.edit

AGCGTGGTCGCGGCCGAGGTCNAGGA

62 16483.edit

TCGAGCGGCCGCCCGGGCAGGTCCACCACCCCAATTCCTTGCTGGTATCATGGCAGCCGCCACGTGCCAGGAT TACCGGCTACATCATCAAGTATGAGAAGCCTGGGTCTCCTCCCAGAGAAGTGGTCCCTCGGCCCCGCCCTGGTG TCACAGAGGCTACTATTACTGGCCTGGAACCGGGAACCGGAATATACAATTTATGTCATTGCCCTGAAGAATAAT CAGAAGAGCGAGCCCCTGATTGGAAGGAAAAAGACAGACGAGCTTCCCCAACTGGTAACCCTTCCACACCCCAA TCTTCATGGACCAGAGATCTTGGATGTTCCTTCCACAGGTTCAAAAGACCCCTTTCGTCACCCCCCCACCCTGGGTATG ACACTGGAAATGGTATTCAGCTTCCTGGCACTTCTGGTCAGCAACCCAGTGTTGGGCCAACAAATGATCTTTGAG GAACATGGTTTTAGGCGGACCACACCGCCCACAACGGGCACCCCCATAAGGNATAGGCCAAGACCATACCCGC CGAATGTAGGACAAGAAGCTCTNTCTCAACAACCATCTCATGGGCCCCATTCCAGGACACTTCTGAGTACATCA TTTCATGTCATCCTGGTGGGCACCTTGATGAANAACCCTTACAGTTCAGGGTTCCTGGAACTTCTACCAGNGCCA CTTCTGACAGGACACTTCTGAGCACCCCT

Fig. 1500

SUBSTITUTE SHEET (RULE 26)

76/101 63 16500.edit

AGCGTGGTCGCGGCCGAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCAATCTTGTAGTTCACACCATTG
TCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCCAAAGCCTAAGCACTGGCACAACAGTTTAAA
GCCTGATTCAGACATTCGTTCCCACTCATCTCCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGAGT
CATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGCCTC
TGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTGCCCGGGCGCCCCGCT
CGA

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Fig. 15PP

77/101

16501.edit

16501.2.edit

GAGGACTGGCTCAGCTCCCAGTATAGCCGCTCTCTGTCCAGTCCAGGACCAGTGGGATCAAGGCGGAGGGTGCA GATGGCGTCCACTCCAGTGGCTGCCCCATGTTTCTCAAGTCTGAGCAAAGNCAGTCTGCAGCCAGAGTACAGAG GGCCAACACTGGTGCTCTTGAACAGGGACCTGAGCAGGCCCTGAAGGACCCTCTCCGTGGTGTTGAACTTCCTG GAGCCAGGGTGCTGCATGTTCTCCTCATACCGCAGGTTGTTGATGGTGAAGTTCAGTGTGAATGGCTCCTCGCT GACCACCC

16502.1.edit

16502.2.edit

TCGAGCGGCCGCCCGGGCAGGTCCTGTCAGAGTGGCACTGGTAGAAGTTCCAGGAACCCTGAACTGTAAGGGTT
CTTCATCAGTGCCAACAGGATGACATGAAATGATGTACTCAGAAGTGTCCTGGAATGGGGCCCATGAGATGGTT
GTCTGAGAGAGAGGCTTCTTGTCCTACATTCGGCGGGTATGGTCTTGGCCCTATGCCTTATGGGGGTGGCCGTTGT
GGGCGGTGTGGTCCGCCTAAAACCATGTTCCTCAAAGATCATTTGTTGCCCAACACTGGGTTGCTGACCAGAAG
TGCCAGGAAGCTGAATACCATTTCCAGTGTCATACCCAGGGNGGGTGACCAAAGGGGGTCNTTTNGACCTGGNG
AAAGGAACCATCCAAAANCTCTGNCCCATG

Fig. 15QQ

78/101 16503.1.edit

16503.2.edit

AAGCGGCCGCCCGGGCAGGNNCAGNAGTGCCTTCGGGACTGGGNTCACCCCCAGGTCTGCGGCAGTTGTCACAG
CGCCAGCCCCGCTGGCCTCCAAAGCATGTGCAGGAGCAAATGGCACCGAGATATTCCTTCTGCCACTGTTCTCC
TACGTGGTATGTCTTCCCATCATCGTAACACGTTGCCTCATGAGGGTCACACTTGAATTCTCCTTTTCCGTTCC
CAAGACATGTGCAGCTCATTTGGCTGGCTCTATAGTTTGGGGAAAGTTTGTTGAAACTGTGCCACTGACCTTTA
CTTCCTCCTTCTCTACTGGAGCTTTCCGTACCTTCCACTTCTGCTGNTGGNAAAAAGGGNGGAACNTCTTATCA
ATTTCATTGGACAGTANCCCNCTTTCTNCCCAAAACATNCAAGGGAAAATATTGATTNCNAGAGCGGATTAAGG
AACAACCCNAATTATGGGGGCCCAGAAATAAAAGGGGGCTTTTCCACAGGTNTTTTCCT

16504.1.edit

TCGAGCGGCCGCCCGGGCAGGTCTGCAGGCTATTGTAAGTGTTCTGAGCACATATGAGATAACCTGGGCCAAGC
TATGATGTTCGATACGTTAGGTGTATTAAATGCACTTTTGACTGCCATCTCAGTGGATGACAGCCTTCTCACTG
ACAGCAGAGATCTTCCTCACTGTGCCAGTGGGCAGGAGAAAGAGCATGCTGCGACTGGACCTCGGCCGCCGACCA
CGCT

16504.2.edit

AGCGTGGTCGCGGCCGAGGTCCAGTCGCAGCATGCTCTTTCTCCTGCCCACTGGCACAGTGAGGAAGATCTCTG CTGTCAGTGAGAAGGCTGTCATCCACTGAGATGGCAGTCAAAAGTGCATTTAATACACCTAACGTATCGAACAT CATAGCTTGGCCCAGGTTATCTCATATGTGCTCAGAACACTTACAATAGCCTGCAGACCTGCCCGGGCGGCCGC TCGA

Fig. 15RR

79/101

16505.1.edit

CGAGCGGCCGCCGGGCAGGTCCAGACTCCAATCCAGAGAACCACCAAGCCAGATGTCAGAAGCTACACCATCA CAGGTTTACAACCAGGCACTGACTACAAGATCTACCTGTACACCTTGAATGACAATGCTCGGAGCTCCCCTGTG GTCATCGACGCCTCCACTGCCATTGATGCACCATCCAACCTGCGTTTCCTGGCCACCACCACCCCAATTCCTTGCT GGTATCATGGCAGCCGCCACGTGCCAGGATTACCGGCTACATCATCAAGTATGAGAAGCCTGGGTCTCCTCCCA GAGAAGTGGTCCCTCGGCCCCCTGGTGNCACAGAAGCTACTATTACTGGCCTGGAACCGGGAACCGAATAT ACAATTTATGTCATTGCCCTGAAGAAATAATCANAAGAGCGAGCCCCTGATTGGAAGG

16505.2.edit

16506.1.edit

16506.2.edit

AGCGTGGTCGCGGCCGAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATCGG
TCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCACA
CTGGGCTGAGTGGGGTACACCGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTGCA
GCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGTGC
GGGCGGGGTTCTTGCGGCTGCCCTCTGGGCTCCGGATGTTCTCGATCTGCTGGCTCAAGCTCTTGAAGGGTGGT
GTCCACCTCGAGGTCACGGACCGCAAACCTGCCCGGGCGCCGCTCGA

Fig. 15SS

80/101

16507.1.edit

16507.2.edit

TCGAGCGCCCCGGGCAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATC
GGTCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCA
CACTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTG
CAGCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGT
GCGGGCGGGGTTCTTGACCTCGGCCGCGACCACGCT

16508.1.edit

16508.2.edit

Fig. 15TT

81/101

16509.1.edit

AGCGTGGTCGCGGCCGAGGTCTGGGATGCTCCTGCTGTCACAGTGAGATATTACAGGATCACTTACGGAGAAAC
AGGAGGAAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGGAGCAAGTCTACAGCTACCATCAGCGGCCTTAAAC
CTGGAGTTGATTATACCATCACTGTGTATGCTGTCACTGGCCGTGGAGACAGCCCCGCAAGCAGCCAAGCCAATT
TCCATTAATTACCGAACAGAAATTGACAAACCATCCCAGATGCAAGTGACCGATGTTCAGGACCAACAGCATTAG
TGTCAAGTGGCTGCCTTCAAGTTCCCCTGTTACTGGTTACAGAAGTAACCACCACTCCCAAAAATGGACCAGGA
CCAACAAAAACTAAAACTGCAGGTCCAGATCAAACAGAAAATGGACTATTGAAGGCTTGCAGCCCACAGTGGAA
GTATGTGGNTAGGNGTCTATGCTCAGAATCCCAAGCCGGAGAAAGTCAGCCTTCTGGTTTAGACTGCAGTAACC
AACATTGATCGCCCTAAAGGACTGGNCATTCACTTGGATGGTGGATGTCCAATTC

16509.2.edit

16510.1.edit

16510.2.edit

AGCGTGGTCGCGGCCGAGGTCTGGGATGCTCCTGCTGTCACAGTGAGATATTACAGGATCACTTACGGAGAAAC
AGGAGGAAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGGAGCAAGTCTACAGCTACCATCAGCGGCCTTAAAC
CTGGAGTTGATTATACCATCACTGTGTATGCTGTCACTGGCCGTGGAGACAGCCCCGCAAGCAGTAAGCCAATT
TCCATTAATTACCGAACAGAAATTGACAAACCATCCCAGATGCAAGTGACCGATGTTCAGGACAACAGCATTAG
TGTCAAGTGGCTGCCTTCAAGTTCCCCTGTTACTGGTTACAGAGTAACCACCACTCCCAAAAATGGGACCAGGA
CCAACAAAAAACTAAAACTGCANGGTCCAGATCAAACAGAAATGACTATTGAAGGCTTGCAGCCCACAGTGGAG
TATGTGGGTTAGTGTCTATGCTCAGAATNCCAAGCGGAGAGAGTCAGCCTCTGGTTCAGACT

Fig. 15UU

82/101

16511.1.edit

16511.2.edit

AGCGTGGTCGCGGCCGAGGTCTGTAGCTTCTGTGGGACTTCCACTGCTCAGGCGTCAGGCTCAGGTAGCTGCTG
GCCGCGTACTTGTTGTTGCTTTGNTTGGAGGGTGTGGTGGTCTCCACTCCCGCCTTGACGGGGCTGCTATCTGC
CTTCCAGGCCACTGTCACGGCTCCCGGGTAGAAGTCACTTATGAGACACACCAGTGTGGCCTTGTTGGCTTGAA
GCTCCTCAGAGGAGGGGGGAACAGAGTGACCGAGGGGGCAGCCTTGGGCTGACCTAGGACGGTCAGCTTGGTC
CCTCCGCCGAACACCCCAATTGTTGTTGCCTGCATATGAGCTGCAGTAATAATCAGCCTCATCCTCAGCCTGGAG
CCCAGAGACNGTCAAGGGAGGCCCGTGTTTGCCAAGACTTGGAAGCCAGANAAGCGATCAGGGACCCCTGAGGG
CCGCTTTACNGACCTCAAAAAATCATGAATTTGGGGGGGCCTTTGCCTGGGNGTTGGTTAGTNACCAGNAAAACA
AAATTTCATAAAGCACCAACGTCACTGCTGGTTTCCAGTGCANGAANATGGTGAACTGAANTGTCC

16512.1.edit

16512.2.edit.

TCGAGCGCCCCCGGGCAGGTCCATACAGGGCTGTTGCCCAGGCCCTAGAGGNCATTCCTTGTACCCTGATCC AGAACTGTGGGACCAGCACCACCCAGCACCACCCCAGGAGAACTGTGAGACC TGGGGTGTAAATGGNGAGACCGGGTACTTTGGTGGACATGAAGGAACTGGGGCATATGGGAGCCATTGGCTGNGAA GCTGCANACTTATAAGACAGCAGTGGAGACGGCAGTTCTGCTACTGCGAATTGATGACATCGTTTCAGGCCACA AAAAGAAAGGCGATGACCANAGCCGGCAAGGCGGGGCTTCCTGATGCTGGACCTCGGCCGCCGACCACGCTT

Fig. 15VV

83/101

16514.1.edit

AGCGTGGTCGCGGCCGAGGTCCACTAGAGGTCTGTGTGCCATTGCCCAGGCAGAGTCTCTGCGTTACAAACTCC
TAGGAGGGCTTGCTGTGCGGAGGGCCTGCTATGGTGTGCTGCGGTTCATCATGGAGAGTGGGGCCAAAGGCTGC
GAGGTTGTGGTGTCTGGGAAACTCCGAGGACAGAGGGCTAAATCCATGAAGTTTGTGGATGGCCTGATGATCCA
CAGCGGAGACCCTGTTAACTACTACGTTGACACTGCTGTGCGCCACGTGTTGCTCANACAGGGTGTGCTGGGCA
TCAAGGTGAAGATCATGCTGCCCTGGGACCCANCTGGCAAAAAATGGCCCTTAAAAAACCCCTTGCCNTGACCACG
TGAACCATTTGTGNGAACCCCCAAGATGAANATACTTGCCCACCCCCCCATTC

16514.2.edit

16515.1.edit

AGCGTGGTCGCGGCCGAGGTCTGGCCCTCCTGGCAAGGCTGGTGAAGATGGTCACCCTGGAAAACCCGGACGAC CTGGTGAGAGAGAGGCTGTTTGGACCACACACAGGGTGCTCGTGGTTTCCCTGGAACTCCTGGACTTCCTGGCTTCAAA GGCATTAGGGGACACACAATGGTCTGGATGGATTGAAGGGACAGCCCGGTGCTCCTGGTGTAAAGGGGTGAACCTGG NGCCCCTGGTGAAAATGGAACTCCAGGTCAAACAGGAGCCCGNGGGCTTCCTGGNGAGAGAGAGGACGTGTTGGTG CCCCTGGCCCANACCTGCCCGGGCCGCTCNAAAAAGCCCGAAATCCAGNACACTGGCGGCCGNTACTANTGGA ATCCGAACTTCGGTACCAAAGCTTGGCCGTAATCATGGCCATAGCTTGTTCCCTGGGGGGGAAATTGGTATTCC GCTNCCAATTCCACACACACATACCGAACCCGGAAAGCATTAAAGTGTAAAAGCCCTGGGGGGGCCTAAATGANG TGAGCNTAACTCNCATTTAATTGGCGTTGCGCTTCACTGCCCCGCTTTTCCAGTCCGGGNA

16515.2.edit

TCGAGCGGCCCCGGGCAGGTCTGGGCCAGGGGCACCAACACGTCCTCTCACCAGGAAGCCCACGGGCTCC
TGTTTGACCTGGAGTTCCATTTTCACCAGGGGCACCAGGTTCACCCTTCACACCAGGAGCACCGGGCTGTCCCT
TCAATCCATCCAGACCATTGTGNCCCCTAATGCCTTTGAAGCCAGGAAGTCCAGGAGTTCCAGGGAAACCACGA
GCACCCTGTGGTCCAACAACTCCTCTCTCACCAGGTCGTCCGGGTTTTCCAGGGTGACCATCTTCACCAGCCTT
GCCAGGAGGGCCAGACCTCGGCCGCGACCACGCT

Fig. 15WW

84/101

16516.1.edit

ANCGTGGTCGCGGCCGAGGTCCTCACCAGAGGTGNCACCTACAACATCATAGTGGAGGCACTGAAAGACCANCAGAGGCATAAGGTTCGGGAAGAGG

16516.2.edit

TCGAGCGCCCCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCAATCTTGTAGTTCACACCAT TGTCATGGCACCACTCTGAAATGACCACTTCCCAAAGCCTAAGCACTGGCACAACAGTTTA AAGCCTGATTCAGACATTCGTTCCCACTCCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGTCCACGGTAACAACCTCTTCCCGAACCTTATGCC TCTGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTCNGNCCNGAACAAC GCTTAAGCCCGNATTCTGCAGAATAATCCCATCACACTTGGCGGCCGCTTCGANCATGCATCNTAAAAAGGGGCC CCAATTTCCCCCTTATAAGNGAANCCGTATTTNCCAATTTCACTGGNCCCGCCGNTTTTACAAACGNCGGTGAA CTGGGGGAAAAAACCCTGGCGGTTACCCAACTTTAATCGCCNTTGGCAGCACAATCCCCCCTTTTCGNCCANCNTG GGCGTAAATAACCGAAAA

16517.1.edit

16518.1.edit

AGCGTGGTCGCGGCCGAGGTCTGAGGTTACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGT
TCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACG
TACCGGGNGGTCAGCGTCCTCACCGTCCTGCACCAGAATTGGTTGAATGGCAAGGAGTACAAGNGCAAGGTTTC
CAACAAAGCCNTCCCAGCCCCCNTCGAAAAAACCATTTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGT
ACACCCTGCCCCCATCCCGGGAGGAAAAGANCAANAACCNGGTTCAGCCTTAACTTGCTTGGTCNAANGCTTTT
TATCCCAACGNACTTCCCCCNTGGAANTGGGAAAAACCAATGGGCCAANCCGAAAAACAATTACAANAACCCC

16518.2.edit

Fig. 15XX

85/101

16519.1.edit

AGCGTGGTCGCGGACGANGTCCTGTCAGAGTGGNACTGGTAGAAGTTCCANGAACCCTGAACTGTAAGGGTTCT TCATCAGTGCCAACAGGATGACATGAAATGATGTACTCAGAAGNGNCCTGGAATGGGGCCCATGANATGGTTGC C

16519.2.edit

TCGAGCGCCCCCGGGCAGGTCCACCACCCCAATTCCTTGCTGGTATCATGGCAGCCGCCACGTGCCAGGAT TACCGGCTACATCATCAAGTATGAGAAGCCTGGGTCTCCTCCCAGAGAAGTGGTCCCTCGGCCCCGCCCTGGTG TCACAGAGGCTACTATTACTGGCCTGGAACCGGGAACCGGAATATACAATTTATGTCATTGCCCTGAAGAATAAT CAGAAGAGCGAGCCCCTGATTGGAAGGAAAAAGACAGACGAGCTTCCCCAACTGGTAACCCTTCCACACCCCAA TCTTCATGGACCAGAGATCTTGGATGTTCCTTCCACAGTTCAAAAGACCCCTTTCGGCACCCCCCTGGGTATG AACCTGGGAAAANGGNANTTAANCTTTCCTGGCA

16520.1.edit

AGCGTGGTCGCGGCCGAGGTCTGGGATGCTCCTGCTGTCACAGTGAGATATTACAGGATCACTTACGGAGAAAC
AGGAGGAAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGGAGCAAGTCTACAGCTACCATCAGCGGCCTTAAAC
CTGGAGTTGATTATACCATCACTGTGTATGCTGTCACTGGCCGTGGAGACAGCCCCGCAAGCAGCAAGCCAATT
TCCATTAATTACCGAACAGAAATTGACAAACCATCCCAGATGCAAGTGACCGATGTTCAGGACAACAGCATTAG
TGTCAAGTGGCTGCCTTCAAGGTNCCCTGGTACTGGGTTACAGANTAACCACCACTCCCAAAAATGGACCAGGA
ACCACAAAAACTTAAACTGCAGGGTCCAGATCAAAACAGAAATGACTATTGAANGCTTGCAGCCCACAGTGGGA
GTATGNGGGTAGTGNCTATGCTTCAGAATCCAAGCGGAAAAANGTCAAGCCTTNTGGGTTCAA

16520.2.edit

TCGAGCGGCCGGGCAGGTCCTTGCAGCTCTGCAGTGTCTTCTTCACCATCAGGTGCAGGGAATAGCTCAT GGATTCCATCCTCAGGGCTCGAGTAGGTCACCTGTACCTGGAAACTTGCCCCTGTGGGCTTTCCCAAGCAATT TTGATGGAATCGACATCCACATCAGTGAATGCCAGTCCTTTAGGGCGATCAATGTTGGTTACTGCAGNCTGAAC CAGAGGCTGACTCTCTCCGCTTGGATTCTGAGCATAGACACTAACCACATACTCCACTGTGGGCTGCAANCCTT CAATAANNCATTTCTGTTTGATCTGGACC

16521.2.edit

TCGAGCGGCCGGGCAGGTCTGGTGGGGTCCTGGCACACGCACATGGGGGNGTTGNTCTNATCCAGCTGCC CAGCCCCCATTGGCGAGTTTGAGAAGGTGTGCAGCAATGACAACAANACCTTCGACTCTTCCTGCCACTTCTTT GCCACAAAGTGCACCCTGGAGGGCACCAAGAAGGGCCACAAGCTCCACCTGGACTACATCGGGCCTTGCAAATA CATCCCCCCTTGCCTGGACTCTGAGCTGACCGAATTCCCCCTTGCGCATGCGGGACTGGCTCAAGAACCGTCCT GGCACCCTTGTATGANAGGGATGAAGACACNACCC

Fig. 15YY

86/101

16522.1.edit

16522.2.edit

TCGAGCGCCCCCGGGCAGGTTTGGAAGGGGGATGCGGGGGAAGAGAAGACTGACGGTCCCCCCAGGAGTTC AGGTGCTGGGCACGGTGGGCATGTTGTGAGTTTTGTCACAAGATTTTGGCCTCAACTCTCTTGTCCACCTTGGTGT TGCTGGGCTTGTGATCTACGTTGCAGGTGTAGGTCTGGGNGCCGAAGTTGCTGGAGGGCACGGTCACCACGCTG CTGAGGGAGTAGAGTCCTGAGGACTGTANGACAGACCTCGGCCGNGACCACGCTAAGCCGAATTCTGCAGATAT CCATCACACTGGCGGCCGCTCCGAGCATGCATTTTAGAGG

16523.1.edit

AGCGTGGNCGCGGACGANGACAACAACCCC

16523.2.edit

TCGAGCGGCCGCCCGGGCAGGNCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATC
GGTCATGCTCTTGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGNACCAGTTCTTCTGGGCCA
CACTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTG
CAGCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGT
GCGGGCGGGGTTCTTGACCT

16524.1.edit

AGCGTGGTCGCGGCCGAGGTCCAGCCTGGAGATAANGGTGAAGGTGGTGCCCCCGGACTTCCAGGTATAGCTGG ACCTCGTGGTAGCCCTGGTGAGAGAGGGGGTGAAACTGGCCCTCCAGGACCTGCTGGTTTCCCTGGTGCTCCTGGAC AGAATGGTGAACCTGGNGGTAAAGGAGAAAGAGGGGCTCCGGNTGANAAAGGTGAAGGAGGCCCTCCTGNATTG GCAGGGGCCCCANGACTTAGAGGTGGAGCTGGCCCCCCTGGCCCCCGAAGGAGGAAAGGGTGCTGCTGGTCCTCC TGGGCCACCTGG

Fig. 15ZZ

87/101

16524.2.edit

TCGAGCGGCCGCCCGGGCAGGTCTGGGCCAGGAGGACCAATAGGACCAGTAGGACCCCTTGGGCCATCTTTCCC
TGGGACACCATCAGCACCTGGACCGCCTGGTTCACCCTTGTCACCCTTTGGACCAGGACTTCCAAGACCTCCTC
TTTCTCCAGGCATTCCTTGCAGACCAGGAGTACCANCAGCACCAGGTGGCCCAGGAGGACCAGCACCCTTT
CCTCCTTCGGGACCAGGGGGACCAGCTCCACCTCTAAGTCCTGGGGCCCCTGCCAATCCAGGAGGGCCTCCTTC
ACCTTTCTCACCCGGAGCCCCTCTTTCT

16526.1.edit

TCGAGCGGCCCCGGGCAGGTCCACCGGGATATTCGGGGGGTCTGGCAGGAATGGGAGGCATCCAGAACGAGAA GGAGACCATGCAAAGCCTGAACGACCCCTGGCCTCTTACCTGGACAGAGTGAGGAGCCTGGAGACCGACAACC GGAGGCTGGAGAGCAAAATCCGGGAGCACTTGGAGAAGAAGAGGGACCCCAGGTCAGAGACTGGAGCCATTACTTC AAGATCATCGAGGACCTGAGGGCTCANATCTTCGCAAATACTGCNGACAATGCCCG

16526.2.edit

ATGCGNGGTCGCGGCCGANGACCANCTCTGGCTCATACTTGACTCTAAAGNCNTCACCAGNANTTACGGNCATT GCCAATCTGCAGAACGATGCGGGCATTGTCCGCANTATTTGCGAAGATCTGAGCCCTCAGGNCCTCGATGATCT TGAAGTAANGGCTCCAGTCTCTGACCTGGGGTCCCTTCTTCTCCAAGTGCTCCCGGATTTTGCTCTCCAGCCTC CGGTTCTCCGGTCTCCAAGNCTTCTCACTCTGTCCAGGAAAAGAGGCCAGGCGGNCGATCAGGGCTTTTGCATGG ACT

16527.1.edit

16527.2.edit

TCGAGCGCCCCGGGCAGGTCTGCCAACACCAAGATTGGCCCCCGCCGCATCCACACAGTTNGTGTGCGGGG AGGTAACAAGAAATACCGTGCCCTGAGGNTGGACGNGGGGGAATTTCTCCTGGGGCTCAGAGTGTTGTACTCGTA AAACAAGGATCATCGATGTTGTCTACAATGCATCTAATAACGAGCTGGTTCGTACCAAGACCCTGGTGAAGAAT TGCATCGTGCTCATNGACAGCACACCGTACCGACAGTGGGTACCGAAGTCCCACTATGCNCCT

Fig. 15AAA

SUBSTITUTE SHEET (RULE 26)

88/101

16528.1.edit

TCGAGCGCCCCGGGCAGGTCCACCACACCCAATTCCTTGCTGGTATCATGGCAGCCGCCACGTGCCAGGAT TACCGGCTACATCAAGTATGAGAAGCCTGGGTCTCCTCCCAGAGAAGTGGTCCCTCGGCCCCGCCTGGTG TCACAGAGGCTACTATTACTGGCCTGGAACCGGAACCGAATATACAATTTATGTCATTGCCCTGAAG

16528.2.edit

AGCGTGNTCNCGGCCGAGGATGGGGAAGCTCGNCTGTCTTTTTTCCTTCCAATCAGGGGCTNNNTCTTCTGATTA
TTCTTCAGGGCAANGACATAAATTGTATATTCGGNTCCCGGTTCCAGNCCAGTAATAGTAGCCTCTGTGACACC
AGGGCGGGCCGAGGGACCACTTCTCTGGGAGGAGACCCAGGCTTCTCATACTTGATGATGAAGCCGGTAATCC
TGGCACGTGGGCGGCTGCCATGATACCACCAANGAATTGGGTGTGGTGGACCTGCCCGGGCGGCCGCTCGAAA
ANCCGAATTCNTGCAAGAATATCCATCACACTTGGGCGGCCGNTCGAACCATGCATCNTAAAAGGGCCCCAAT
TTCCCCCCTATTAGGNGAAGCCNCATTTAACAAATTCCACTTGG

16529.1.edit

16529.2.edit

AGCGTGGTCGCGGCCGAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATCGG
TCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCACA
CTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTGCA
GCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAAGTGGCACATCTTGAGGTCACGGCAGGGT
GCGGGCGGGGTTCTTGCGGGCTGCCCTTCTGGGCTCCCGGAATGTTCTNNGAACTTGCTGG

Fig. 15BBB

89/101

16530.1.edit

16530.2.edit

16531.1.edit

TCGAGCGCCCCCGGGCAGGTGTTTCAGAGGTTCCAAGGTCCACTGTGGAGGTCCCAGGAGTGCTGGTGGGGCACAGAGGTCCGAGGGTGAAACCATTGACATAGAGACTGTTCCTGTCCAGGGTGTAGGGGCCCAGCTCTTTGATGCCATTGGCCAGTTGGCTCAGCTCCCAGTACAGCCGCTCTCTGTTGAGTCCAGGGCTTTTGGGGTCAAGATGATGCAGTGCAGTCCACTCCAGTGGCTGCTCCATCCTTCTCGGACCTGAGAGAGGGTCAGTCTGCAGCCAGAGTACAGAGGGCCAACACTGGTGTTCTTTGAATA

16531.2.edit

16532.1.edit

Fig. 15CCC

90/101 01_16558.3.edit

AGCGTGGTCGCGGCCGAGGTGAGCCACAGGTGACCGGGGCTGAAGCTGGGGCTGCTGGNCCTGCTGGTCCTG

02_16558.4.edit

03 16535.1.edit

TCGAGCGGTCGCCCGGGCAGGTCCACCGGGATAGCCGGGGGTCTGGCAGGAATGGGAGGCATCCAGAACGAGAA GGAGACCATGCAAAGCCTGAACGACCGCCTGGCCTCTTACCTGGACAGAGTGAGGAGCCTGGAGACCGANAACC GGAGGCTGGANAGCAAAATCCGGGAGCACTTGGAGAAGAAGGGACCCCAGGTCAAGAGACTGGAGCCATTACTT CAAGATCATCGAGGGACCTGGAGG

04_16535.2.edit

AGCGNGGTCGCGGCCGAGGTCCAGCTCTGTCTCATACTTGACTCTAAAGTCATCAGCAGCAAGACGGGCATTGT CAATCTGCAGAACGATGCGGGCATTGTCCGCAGTATTTGCGAAGATCTGAGCCCTCAGGTCCTCGATGATCTTG AAGTAATGGCTCCAGTCTCTGACCTGGGGTCCCTTCTTCTCCAAGTGCTCCCGGATTTTGCTCCCAGCCTCCG GTTCTCGGTCTCCAGGCTCCTCACTCTGTCCAGGTAAGAAGGCCCAGGCGGTCGTTCAGGCTTTGCATGGTCTC CTTCTCGTTCTGGATGCCTCCCATTCCTGCCAGACCC

05 16536.1.edit

TCGAGCGGCCGCCCGGGCAGGTCAGGAAGCACATTGGTCTTAGAGCCACTGCCTCCTGGATTCCACCTGTGCTG
CGGACATCTCCAGGGAGTGCAGAAGGGAAGCAGGTCAAACTGCTCAGATCAGACTAGACTGCTGTTCTCAGTTC
TCACCTGAGCAAGGTCAGTCTGCAGCCAGAGTACAGAGGGCCAACACTGGTGTTCTTGAACAAGGGCTTGAGCA
GACCCTGCAGAACCCTCTTCCGTGGTGTTGAACTTCCTGGAAACCAGGGTGTTGCATGTTTTTCCTCATAATGC
AAGGTTGGTGATGG

Fig. 15DDD

SUBSTITUTE SHEET (RULE 26)

91/101 07_16537.1.edit

08_16537.2.edit

Fig. 15EEE

92/101

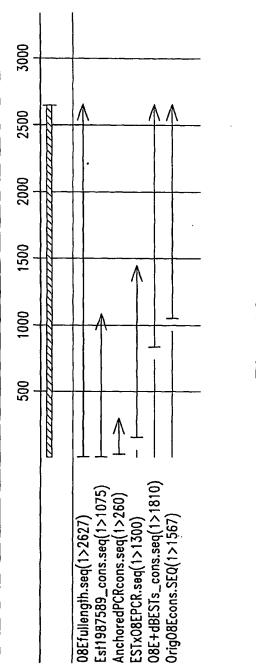


Fig. 16

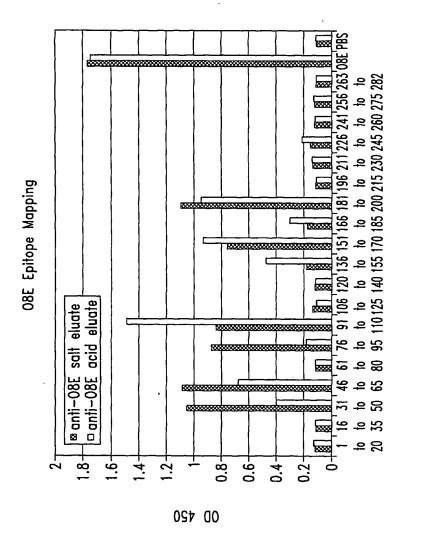
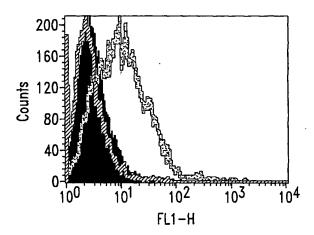


FIG. 17

94/101

08E Surface Expression

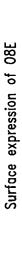


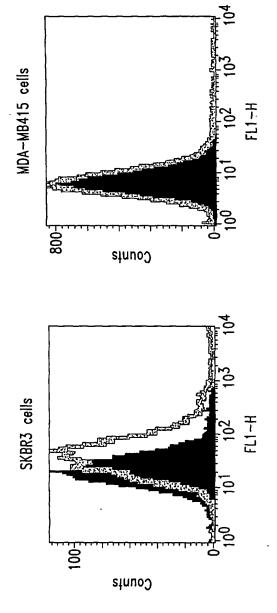
B305D/HEK stained with anti-08E antibody

08E/HEK stained with anti-08E antibody

08E/HEK stained with an irrelevant antibody

Fig. 18

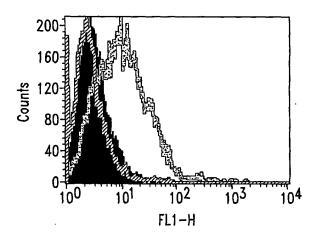




Black; irrelevant antibody Light gray; anti-08E antibody

Fig 19

O8E Surface Expression

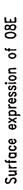


B305D/HEK stained with anti-08E antibody

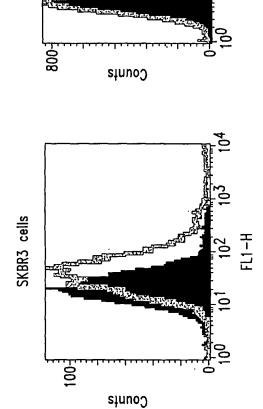
08E/HEK stained with anti-08E antibody

08E/HEK stained with an irrelevant antibody

Fig. 20



MDA-MB415 cells



Black; Irrelevant antibody Light Grey; Anti-08E antibody

FL1-H

Fig 21

98/101

O8E expression in HEK293 Cells (probed with anti-08E rabbit polyclonal sera #2333L)



Fig. 22

99/101

08E Rabbits 01212000

						99	1/1	UΊ					
	1:2048000	0.07	0.07	0.07	0.15	0.16	0.16	0.07	0.07	0.07	0.14	0.14	0.14
	1:1024000	0.07	90.0	90.0	0.24	0.23	0.23	0.07	0.07	0.07	0.20	0.20	0.20
	1:512000	0.07	0.07	0.07	0.40	0.40	0.40	0.07	0.07	0.07	0.32	0.35	0.33
	1:256000	0.07	90.0	0.07	99.0	99.0	0.67	0.07	0.07	0.07	0.58	0.58	0.58
Antibody Ullutions	1:128000 1:256000	90.0	90.0	90.0	1.01	1.00	1.00	0.07	0.07	0.07	0.92	0.88	0.00
	1:64000		0.07	0.07	19.	1.57	1.59	0.07	0.07	6:0	14.	1.44	1.43
	1:32000 1	0.07	0.07	0.07	7.08	2.08	7.08	0.07	0.07	0.07	1.78	1.93	1.85
	1.169	0.07	. 0.07	0.07	2.58	2.48	2.53	0.0	0.10	89.0	2.30	2.37	2.33
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	1:2000	9.0	0.08	89.	2.81	111	279	10.0	0.07	0.07	2.75	2.76	7.76
	1:1000 1:	0.13	0.10	0.1	2.92	2.93	2.93	0.03	0.08	9.08	2.73	2.73	2.73
sera sample		Preimmune sera (#2576L):11/10/99		Average	α-08E (#2576K):1/11/2000	- 1	Average	Preimmune sera (#2333L):11/10/99		Average	α-08E (#2333L):1/11/2000		· Average
Antigen	on Plate	380	(#632-24)				•	-					·

FIG. 20

affi-pure 08E #2576L 739.87A&B

	Date: 5/2/2000	
Antibody Name	08E polyclonal	
Rabbit #, Bleed Date	2576L, 1/11/2000	
Purification Method	affinity	
Buffer	PBS	
Notebook	#705, p150	
fof #	739.87A	739.87B
Antibody Concentration	1.4mg/ml	1.7mg/ml
Initial Amount	18mg	3mg

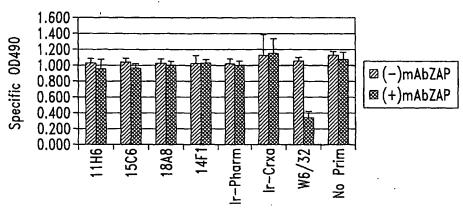
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Antigen	Sera Sample							Antibody	Antibody Dilutions	S			
on Plate		1:108	1:2000	1:4000	1:800 008:1	1:16000	1:32000	1:64000	1:128000	1:256000	1:512000	1:1024000	1:2048000
380	preimmune sera (2576L)	0.15	0.11	0.03		0.08	0.07	0.07	0.07	0.07	90.0	0.07	l
#632-24		0.14	0.10	0.03	90.0	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
	Average	0.14	99	8. 8.	90.0	0.07	0.07	0.07	0.07	0.07	90.0	0.07	0.08
	α-08E (2576K):2/8/2000	2.74	2.71	2.63	2.49	2.29	1.87	1.39	0.92	0.57	0.33	0.20	0.14
		2.75	7.68	2.64	2.47	2.26	1.93	1.42	0.94	0.57	0.34	0.21	0.14
	Average	2.73	2.70	2.63	2.48	2.27	1.90	1.41	0.93	0.57	0.34	0.21	0.14
	affinity pure α -08E poly	2.69	7.60	2.50	2.21	1.83	1.34	0.99	0.64	0.38	0.22	0.15	0.11
	salt peak 739-87A	2.59	7.48	2.38	7.71	1.82	1.33	1.00	0.62	0.37	0.22	0.14	0.11
	Average	2.64	2.54	2.44	2.21	1.83	1.34	1.00	0.63	0.37	0.22	0.15	0.11
	affinity pure $\alpha-08E$ poly	2.46	2.39	2.40	2.34	2.08	1.73	1.29	0.81	0.49	0.29	0.19	0.13
	acid peak 739-67B	7.65	37.66	2.61	2.45	214	1.76	1.30	0.82	0.48	0.29	0.19	0.13
	Average	956	2.53	151	9.39	2.11	1.74	1.30	18.0	670	0.79	0.19	0.13

Fig. 24

101/101

Anti-08E mAb Binding to 08E Amino Acids 61-80 Induces Ligand Internalization

Hek Internalization of OBE mAbs



Primary Ab (50ng/well)

Hek/O8E Internalization of O8E mAbs

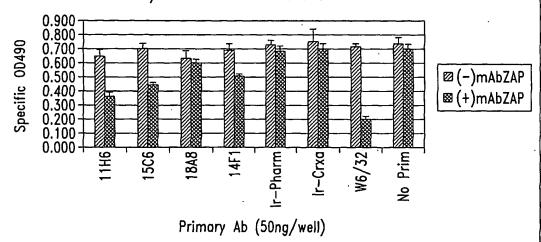


Fig. 25

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Algate, Paul A.
Fling, Steven P.
Retter, Marc W.
Fanger, Gary Richard
Reed, Steven G.
Vedvick, Thomas S.
Carter, Darrick
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Albone, Earl

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PCT/US01/22635

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6

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<211> 448
<212> DNA
<213> Homo sapiens
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WO 02/06317

8

PCT/US01/22635

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<211> 411
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<213> Homo sapiens
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<210> 22
<211> 896
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> 230, 320
<223> n = A, T, C or G
<400> 22
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<210> 23
<211> 111
<212> DNA
<213> Homo sapiens
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<210> 24
<211> 531
<212> DNA
<213> Homo sapiens
<220>
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<221> misc_feature
<222> 472, 494
<223> n = A, T, C or G
<400> 24
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<210> 25
<211> 471
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 377
<223> n = A, T, C or G
<400> 25
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<210> 26
<211> 541
<212> DNA
<213> Homo sapiens
<400> 26
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gtggattttg ctcttttaca acatgtacat ccttactggg ctgtgctgtc acagggatgt 360
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cagtattagc atccacatca gacagcotgg tataaccaga gttggtggtt actgattgta 480
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<210> 27
<211> 461
<212> DNA
<213> Homo sapiens
<220>
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<221> misc feature
<222> 367
<223> n = A, T, C or G
<400> 27
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agtgtgggaa gggggctgga aacaaagtat tcttttcctt caaagcttca ttcctcaagg 180
cctcaattca agcagtcatt gtccttgctt tcaaaagtct gtgtgtgctt catggaaggt 240
atatgtttgt tgccttaatt tgaattgtgg ccaggaaggg tctggagatc taaattcaga 300
gtaagaaaac ctgagctaga actcaggcat ttctcttaca gaacttggct tgcagggtag 360
aatgaangga aagaaactta gaagctcaac aagctgaaga taatcccatc aggcatttcc 420
cataggeett geaactetgt teactgagag atgttateet g
<210> 28
<211> 541
<212> DNA
<213> Homo sapiens
<400> 28
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aactagacaa gtgtgttaag agtgataagt aaaatgcacg tggagacaag tgcatcccca 180
gatctcaggg acctcccct gcctgtcacc tggggagtga gaggacagga tagtgcatgt 240
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<210> 29
<211> 411
<212> DNA
<213> Homo sapiens
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<210> 30
<211> 511
<212> DNA
<213> Homo sapiens
<400> 30
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acagttctgc atggctgaag aggcctcagg aaacttacag tcatggtgga aggcaaagga 180
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 <210> 31
 <211> 827
 <212> DNA
 <213> Homo sapiens
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 <211> 291
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 <213> Homo sapiens
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 <210> 33
 <211> 491
 <212> DNA
 <213> Homo sapiens
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 ttccaaacac actgcacgag aatattgtgg atccgctgtc aggtaagtgt ccgtcactga 180
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 <210> 34
 <211> 521
 <212> DNA
 <213> Homo sapiens
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<223> n = A, T, C or G
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tggatggaaa tgaaaattac ccgtgtcttg tggatgcaga cggtgatgtg atttccttcc 180
caccaataac caacagtgag aagacaaagg ttaagaaaac gacttctgat ttgtttttgg 240
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aaggacgggc cetteettet ggtggtggaa cangteeegg tggtggatet tggaanggaa 480
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                                                                   521
<210> 35
<211> 161
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 18
<223> n = A, T, C or G
<400> 35
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egeogegetg eegacegyea geatgetgee gagagtggge tgeeeegege tgeegetgee 120
gccgccgccg ctgctgccgc tgctgccgct gctgctgctg c
<210> 36
<211> 341
<212> DNA
<213> Homo sapiens
<400> 36
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<210> 37
<211> 521
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 516
\langle 223 \rangle n = A, T, C or G
<400> 37
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tgttgttgtt gatgatgatg atgatgatga taatatttt ctatccccag tgcacaactg 180
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 <210> 38
 <211> 461
 <212> DNA
 <213> Homo sapiens
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 <213> Homo sapiens
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<210> 41
<211> 406
<212> DNA
<213> Homo sapiens
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<400> 41
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<210> 42
<211> 381
<212> DNA
<213> Homo sapiens
<400> 42
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tegeaceage caageettaa etgeetgeet gaeeetgaac cagaaceeag etgaactgee 240
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<210> 43
<211> 451
<212> DNA
<213> Homo sapiens
<400> 43
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aaaatcatta attactttca acttaataac taattgacat teeteaaaag agetgtttte 360
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<210> 44
<211> 521
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agccgtatca gaaatctttt tagggaagca aaggcgaatg ctccttgtgt tatatttatt 180
gatqaattaq attctqttqq tqqqaaqaqa attqaatctc caatqcatcc atattcaaqq 240
cagaccataa atcaacttct tgctgaaatg gatggtttta aacccaatga aggagttatc 300
ataataggag ccacaaactt cccagaggca ttagataatg ccttaatacc gtcctggtcg 360
ttttgacatg caagttacag ttccaaggcc agatgtaaaa ggtcgaacag aaattttgaa 420
atggtatctc aataaaataa agtttgatca atcccgttga tccagaaatt atagcctcga 480
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actetgeact tggteetgeg ettgaggggg ggtgtetaag ttteecettt taaggtttem 540
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<211> 481
<212> DNA
<213> Homo sapiens
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ggcacctggg ccgagcagag caggagactg agggtcagag tggaggctaa gctgccctgg 420
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а
                                                                   481
<210> 47
<211> 461
<212> DNA
<213> Homo sapiens
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<222> 128
<223> n = A, T, C or G
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teaccagtte cecteegtgt eteageagea getgtgagaa atgetttgea tetgtgacet 360
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<210> 48
<211> 571
<212> DNA
<213> Homo sapiens
<400> 48
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agtaagactg gggtccttag atgagaaaga gacacccgag gtccttctct ctgccgtgtg 120
aggatgcatc aagaaggcgg ccgtctgcaa gcgaaggaga ggccgcacca gaaaccgaca 180
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16

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taactgatgg cttcgctgtc ttctgtaaaa attgctatga gagaactttt cactcactgt 360
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cccgtgccag gtacttcacg caccaagctc a
<210> 49
<211> 511
<212> DNA
<213> Homo sapiens
<400> 49
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caacaaatat ccccaaaata aagcaagcat atatatcttg aatgtgtaat aatccagtga 120
taaacaagag cagtacttta aaagaaaaaa aaatatgtat ttctgtcagg ttaaaatgag 180
aatcaaaacc atttactctg ctaactcatt attttttgct ttctttttgg ttaaqagagg 240
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accccagccc ccatttccaa actttaagac cacaaacaag taatttactt ttctgaacat 360
tggttttttc tggaaaatgg gaattataaa atagactttg cagactctta tgagattaaa 420
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ctcaccccgt cacccaggct ggagtacagt g
<210> 50
<211> 561
<212> DNA
<213> Homo sapiens
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tcaacagatt gttgatcacc taccatatgc ttggtattgt tctaattgct ggggatacag 180
caagaggttc tgcagaactt catggagcat gaaagtaaat aaacaaagtt aatttcaagg 240
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gaattttggc caggcatggt g
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<210> 51
<211> 451
<212> DNA
<213> Homo sapiens
<400> 51
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atacagggat tacgcctgtg tatgccgaca cttaaatact gtaccaggac cactgctgtg 120
cttaggtctg tattcagtca ttcagcatgt agatactaaa aatatactgt agtgttcctt 180
taaggaagac tgtacagggt gtgttgcaag atgacattca ccaatttgtg aattatttca 240
acccagaaga tacctttcac tctataaact tgtcataggc aaacatgtgg tgttagcatt 300
gagagatgca cacaaaaatg ttacataaaa gttcagacat tctaatgata agtgaactga 360
aaaaaaaaaa aaccccacat ctcaattttt gtaacaagat aaagaaaata atttaaaaac 420
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<210> 52
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tatttctatg caaaagtatg ccttcaaact gcttaaatga tatatgatat gatacacaaa 180
ccagttttca aatagtaaag ccagtcatct tgcaattgta agaaataggt aaaagattat 240
aagacacctt acacacacac acacacaca acacacacgt gtgcaccgcc aatgacaaaa 300
aacaatttgg cctctcctaa aataagaaca tgaagacct taattgctgc caggagggaa 360
cactgtgtca cccctcccta caatccaggt agtttccttt aatccaatag caaatctggg 420
catatttqaq aggagtqatt ctqacaqcca csqttqaaat cctqtqqqqa accattcatq 480
tocacccact ggtgccctga aaaaatgcca ataatttttc gctcccactt ctgctgctgt 540
ctcttccaca tcctcacata gaccccagac ccgctggccc ctggctgggc atcgcattgc 600
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ggtcggtcat tgtcataacc ag
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<210> 53
<211> 311
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 208
<223> n = A, T, C or G
<400> 53
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tatatettte attatgeeat ettatettet aatgbeaagg gaacagwtge taametgget 120
tetgeattwa teacattaaa aatggettte ttggaaaate ttettgatat gaataaagga 180
tettttavag ccatcattta aagemggntt etetecaaca egagtetget sasggggggk 240
gagetgtgaa etetggetga aggettteee atacacaetg caatgacmtg gtttetgaee 300
agbgtgagtt a
<210> 54
<211> 561
<212> DNA
<213> Homo sapiens
<400> 54
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cctccatcat cgggttcata ctggagagaa accctatgta tgtaatgaat gcggcagagc 120
ctttggtttt aactctcatc ttactgaaca cgtaaggatt cacacaggag aaaaacccta 180
tgtttgtaat gagtgcggca aagcetttcg tcggagttcc actettgttc agcatcgaag 240
agttcacact ggggagaagc cctaccagtg cgttgaatgt gggaaagctt tcagccagag 300
ctcccagctc accctacatc agccgagttc acactggaga gaagccctat gactgtggtg 360
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gagagacteg taagtgeaga aaacatggte cageetttgt teatggetee ageeteacag 480
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tcattctgcg ctggacagtt c
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<210> 55
<211> 811
<212> DNA
<213> Homo sapiens
<400> 55
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cctgttgcct gacaaatgga attgacagcg tatgccatga ctattccatt tqtcaqqcat 660
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qtcctttggc aaaagtaatt qcaacttctt ctaggtattc tattgtccgt tccactggtg 780
gaacccctgg gaccaggact aaaacctcca g
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<210> 56
<211> 591
<212> DNA
<213> Homo sapiens
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<221> misc_feature
\langle 222 \rangle 45, \overline{4}77, 490, 561
<223> n = A, T, C or G
<400> 56
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tacaaagagc tactctatct gaaaaaaaat taaaaaataa atgagacaag atagtttatg 240
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tggcctggaa gataaggaga aagtctcaga aacacactgg tgggaagcaa tcccacnggc 480
cgtgccccan gagcttccca cctgctgctg gctccctggg tggctttggg aacagcttgg 540
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<210> 57
<211> 481
<212> DNA
<213> Homo sapiens
<400> 57
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aattatgatt tatageette teaaataeet geeataettg atateteaae eagagetaat 120
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attttttctg tattaaacct ctatcatagt ttaagcctat tagggtactt aatccttaca 240
aataaacagg tttaaaatca cctcaatagg caactgccct tctggttttc ttctttgact 300
aaacaatctg aatgettaag attttecact ttgggtgeta geagtacaca gtgttacact 360
ctgtattcca gacttcttaa attatagaaa aaggaatgta cactttttgt attctttctg 420
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<210> 58
<211> 141
<212> DNA
<213> Homo sapiens
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<210> 59
<211> 191
<212> DNA
<213> Homo sapiens
<400> 59
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acaaqacttg ggaqtgattc acacctggaa caacatactg gacttcacac tggabagaaa 120
ccttacaagt gtaatgagtg tggcaaagcc tttggcaagc agtcaacact tattcaccat 180
caggcaattc a
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<210> 60
<211> 480
<212> DNA
<213> Homo sapiens
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<210> 61
<211> 381
<212> DNA
<213> Homo sapiens
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<210> 62
<211> 906
<212> DNA
<213> Homo sapiens
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egggeegteg getteteact teetggaeet eeeeggegee egggeetgag gaetggeteg 240
gcggagggag aagaggaaac agacttgagc agctccccgt tgtctcgcaa ctccactgcc 300
gaggaactet cattlettee etegeteett cacececcae eteatgtaga aaggtgetga 360
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20

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agcqtccqqa qqqaaqaaqa acctqqqcta ccqtcctqqc cttcccmccc ccttcccqqg 420
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<211> 491
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<213> Homo sapiens
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<211> 511
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<213> Homo sapiens
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<210> 65
<211> 394
<212> DNA
<213> Homo sapiens
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<210> 66

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  <213> Homo sapiens
  <400> 66
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  atttttccat gaagatgtac ggaaatctga tgttgaatat gaaaatggcc cccaaatgga 180
  attecaaaag gttaccacag gggetgtaag acctagtgac cetectaagt gggaaagagg 240
  aatggagaat agtatttctg atgcatcaag aacatcagaa tataaaactg agatcataat 300
  gaaggaaaat tocatatoca atatgagttt actoagagac agtagaaact attoccagq 359
  <210> 67
  <211> 450
  <212> DNA
  <213> Homo sapiens
  <220>
  <221> misc_feature
  <222> 425
  <223> n = A, T, C or G
  <400> 67
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  taatgeeeet teeteteett etgeaeagga gacacagatg ggtaacatag aggeatggga 120
  agtggaggag gacacaggac tagcccacca ccttctcttc ccggtctccc aagatgactg 180
. cttatagagt ggaggaggca aacaggtccc ctcaatgtac cagatggtca cctatagcac 240
  cagetecaga tggecaegtg gttgeagetg gaeteaatga aaetetgtga caaecagaag 300
  atacctgctt tgggatgaga gggaggataa agccatgcag ggaggatatt taccatccct 360
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  <211> 511
  <212> DNA
  <213> Homo sapiens
  <400> 68
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  cacagcagaa acgccagcag agaaaatggg agccgagagt ccttagccct ggagctgagg 180
  ctgcctctgg gctgacccgc tggctgtacg tggccagaac tggggttggc atctggcatc 240
  catttgaggc cagggtggag gaaagggagg ccaacagagg aaaacctatt cctgctgtga 300
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<211> 414
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<213> Homo sapiens
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<213> Homo sapiens
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ggecetgaag greectetet gtagtgttga actteetgga gecaggeeae atgtteteet 240
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<211> 361
<212> DNA
<213> Homo sapiens
<400> 77
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<211> 356
<212> DNA
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PCT/US01/22635 WO 02/06317

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<213> Homo sapiens
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<221> misc_feature
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<211> 226
<212> DNA
<213> Homo sapiens
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<212> DNA
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<221> misc feature
<222> 23
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<211> 310
<212> DNA
<213> Homo sapiens
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26

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<210> 82
<211> 571
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 202
<223> n = A, T, C or G
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<211> 551
<212> DNA
<213> Homo sapiens
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<212> DNA
<213> Homo sapiens
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<210> 85

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<211> 561
<212> DNA
<213> Homo sapiens
<400> 85
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<211> 795
<212> DNA
<213> Homo sapiens
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<210> 87
<211> 594
<212> DNA
<213> Homo sapiens
<400> 87
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<210> 88
<211> 557
<212> DNA
<213> Homo sapiens
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<210> 89
<211> 561
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> 544, 551
\langle 223 \rangle n = A, T, C or G
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WO 02/06317 PCT/US01/22635

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<212> DNA
<213> Homo sapiens
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cagtaccacc cetetetece caettteeet eteeeggeaa catetetggg aateaacage 180
atattqacac qttqqaqccq aqcctqaaca tqcccctcgq ccccaqcaca tqqaaaaccc 240
cetteettge ctaaggtgte tgagtttetg getettgagg cattteeaga ettgaaatte 300
tcatcagtcc attgctcttg agtctttgca gagaacctca gatcaggtgc acctgggaga 360
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agacattaaa gcaaaaatgc aagcaagtat agaaaaaggt ggttctcttc ccaaagtgga 180
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qttgtccaaa atgcctgttt agtttttaaa gatgqaactc caccctttgc ttggttttaa 480
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<211> 483
<212> DNA
<213> Homo sapiens
<400> 114
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ttgtggaatg tgtttaaagg attgattcta gaacctttgt atatttgata gtatttctaa 180
ctttcatttc tttactqttt qcaqttaatq ttcatqttct qctatqcaat cqtttatatq 240
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<211> 521
<212> DNA
<213> Homo sapiens
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<211> 501
<212> DNA
<213> Homo sapiens
<400> 116
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agetgeette cageageetg ccaaggeeat ggeagagaga gaetgeaaac aaacacaage 180
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<210> 117
<211> 451
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> 320
<223> n = A, T, C or G
<400> 117
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gagattgtcc ctaagtaact gcatgatcag agtgctgkct ttataagact cttcattcag 180
cgtatccaat tcagcaattg cttcatcaaa tgccgttttt gccaggctac aggccttttc 240
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<213> Homo sapiens

WO 02/06317 PCT/US01/22635

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ataatctcct ttcattttca aagtagaaca c
<210> 118
<211> 501
<212> DNA
<213> Homo sapiens
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gggtctttgt tccctgcagc cctcccacgg gaatgacaat ggataaaagt gagctggtac 180
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caatgctaca caacccagaa a
                                                                  501
<210> 119
<211> 391
<212> DNA
<213> Homo sapiens
<400> 119
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tototgatca ggggaaagga gotogaatga gggaggtaga gttggaaagg gaaaggatto 360
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<210> 120
<211> 421
<212> DNA
<213> Homo sapiens
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<221> misc_feature
<222> 409
<223> n = A,T,C or G
<400> 120
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caccgagget gagagcaaca tgaacgacet cgtetetgag tateaagcag taccaggatg 180
ccaccgcaga agaggaggag gatttcggtg aggaggccga agaggaggcc taaggcagag 240
cocceateac cteaggette teagtteect tageegtett acteaactge ccettteete 300
teceteagaa tttgtgtttg etgeetetat ettgtttttt gtttttett etgggggggt 360
ctagaacagt gcctggcaca tagtaggcgc tcaataaata cttggttgnt gaatgtctcc 420
<210> 121
<211> 206
<212> DNA
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gtttccaata aaacggttta ctacct
<210> 122
<211> 131
<212> DNA
<213> Homo sapiens
<400> 122
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gatgacgatg tcgataccaa gaagcagaag accgacgagg atgactagac agcaaaaaag 120
gaaaagttaa a
<210> 123
<211> 231
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 166, 202, 222, 225
<223> n = A, T, C or G
<400> 123
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gcaattacat akcargaagc atgtttgctt tccagaagac tatggnacaa tggtcattwg 180
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<210> 124
<211> 521
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 284, 412, 513
<223> n = A,T,C or G
<400> 124
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atetteagea ggeagetece accaggaett ateteasaaa attgetgace geetgggeet 180
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<210> 125
<211> 341
<212> DNA
<213> Homo sapiens
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<222> 277
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<400> 125
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tttccaaata taaatacgtg tgtcagaact ggaaaatcct ccagcaccca ccacccaage 240
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<210> 126
<211> 521
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 353, 399, 455
<223> n = A, T, C or G
<400> 126
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ggagagatec agcagatece ggtgcagetg aatgccggcc agctgcagta tatccgctta 180
gcccagcctg tatcaggcac tcaagttgtg cagggacaga tccagacact tgccaccaat 240
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<211> 351
<212> DNA
<213> Homo sapiens
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tetettaaat geaaagaatg ttteeatgge etetggatge aaatacaeag agetetgggg 240
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<211> 521
<212> DNA
<213>. Homo sapiens
<400> 128
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taaatatact aatagctaag tcatttgcca gccaggtccc ggtgaacagt agagaacaag 180
gagettgeta agaattaatt ttgetgtttt teaccecatt caaacagage tgeeetgtte 240
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. 40

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cctgatggag ttccattcct gccagggcac ggctgagtaa cacgaagcca ttcaagaaag 300
qcqqqtqtqa aatcactqcc accccatqqa caqacccctc actcttcctt cttagccqca 360
gcgctactta ataaatatat ttatactttg aaattatgat aaccgatttt tcccatgcgg 420
catcctaagg gcacttgcca gctcttatcc ggacagtcaa gcactgttgt tggacaacag 480
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<210> 129
<211> 521
<212> DNA
<213> Homo sapiens
<400> 129
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<213> Homo sapiens
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<210> 131
<211> 341
<212> DNA
<213> Homo sapiens
<400> 131
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<211> 844
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 37
\langle 223 \rangle n = A,T,C or G
<400> 132
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<210> 136
<211> 341
<212> DNA
<213> Homo sapiens
<400> 136
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<211> 551
<212> DNA
<213> Homo sapiens
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<210> 138
<211> 531
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 490
<223> n = A, T, C or G
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<210> 139
<211> 521
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 517
<223> n = A, T, C or G
<400> 139
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ggagaaaggc gggcccggga acaggctgag gctgaggtgg cctccttgaa ccgtaggatc 180
cagetggttg aagaagaget ggacegtget caggagegee tggccactge cetgeaaaag 240
ctggaagaag ctgaaaaagc tgctgatgag agtgagagag gtatgaaggt tattgaaaac 300
cgggccttaa aagatgaaga aaagatggaa ctccaggaaa tccaactcaa agaagctaag 360
cacattgcag aagaggcaga taggaagtat gaagaggtgg ctcgtaagtt ggtgatcatt 420
gaaggagact tggaaccgca cagaaggaac gagcttgagc ttggcaaaag tcccgttgcc 480
cagagatggg atgaaccaga ttagactgat ggaccanaac c
<210> 140
<211> 571
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 7
<223> n = A, T, C or G
<400> 140
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taaactctgc tctgagcctc cttgtcgcct gcatttagat ggctcccgca aagaagggtg 180
gcgagaagaa aaagggccgt tctgccatca acgaagtggt aacccgagaa tacaccatca 240
acattcacaa gcgcatccat ggagtgggct tcaagaagcg tgcacctcgg gcactcaaag 300
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tcaacaaagc tgtctgggcc aaaggaataa ggaatgtgcc ataccgaatc cggtgtgcgg 420
ctgtccagaa aacgtaatga ggatgaagat tcaccaaata agctatatac tttggttacc 480
tatgtacctg ttaccacttt caaaaatcta cagacagtca atgtggatga gaactaatcg 540
ctgatcgtca gatcaaataa agttataaaa t
<210> 141
<211> 531
<212> DNA
<213> Homo sapiens
<400> 141
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aatggggagg cctcttggag acacagaggg tttcaccttg gatgacctct agagaaattg 120
cccaagaagc ccaccttctg gtcccaacct gcagacccca cagcagtcag ttggtcaqqc 180
cctgctgtag aaggtcactt ggctccattg cctgcttcca accaatgggc aggagagaag 240
gcctttattt ctcgcccacc cattcctcct gtaccagcac ctccgttttc agtcagtgtt 300
qtccaqcaac qqtaccqttt acacaqtcac ctcagacaca ccatttcacc tcccttqcca 360
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tcagtccatt ccagttggca ccagcctgaa ccatttggta cctggtgtta actggagtcc 480
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                                                                  531
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<210> 142
  <211> 491
  <212> DNA
  <213> Homo sapiens
· <220>
  <221> misc_feature
  <222> 410
  <223> n = A, T, C or G
  <400> 142
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  ttgtcctgaa accetactgg agaagtcage atgaggcace tactgagaga agtgcccaga 120
  aactgctgac tgcatctgtt aagagttaac agtaaagagg tagaagtgtg tttctgaatc 180
  agagtggaag cgtctcaagg gtcccacagt ggaggtccct gagctacctc ccttccgtga 240
  gtgggaagag tgaagcccat gaagaactga gatgaagcaa ggatggggtt cctgggctcc 300
  aggcaagggc tgtgctctct gcagcaggga gccccacgag tcagaagaaa agaactaatc 360
  atttgttgca agaaaccttg cccggatact agcggaaaac tggaggcggn ggtgggggca 420
  caggaaagtg gaagtgattt gatggagagc agagaagcct atgcacagtg gccgagtcca 480
  cttgtaaagt g
                                                                     491
  <210> 143
  <211> 515
  <212> DNA
  <213> Homo sapiens
  <400> 143
  ttcaagcaat tgtaacaagt atatgtagat tagagtgagc aaaatcatat acaattttca 60
  tttccaqttq ctattttcca aattqttctg taatqtcqtt aaaattactt aaaaattaac 120
  aaagccaaaa attatattta tgacaagaaa gccatcccta cattaatctt acttttccac 180
  teaeeggeee ateteettee tettttteet aactatgeea ttaaaaetgt tetaetggge 240
  egggegtgtg geteatgeet gtaateeeag cattttggga ggeeaaggea ggeggateat 300
  gaggtcaaga gattgagacc atcctggcca acatggtgaa accccgcctc gactaagaat 360
  acaaaaatta getgggeatg gtggegeatg cetgtagtet cagetacteg ggaggetgag 420
  gcagaagaat cgcttgaacc cgggaggcag aggatgcagt gagccccgat cgcgccactg 480
  cactctagcc tgggcgacag actgagactc tgctc
  <210> 144
  <211> 340
  <212> DNA
  <213> Homo sapiens
  <400> 144
  tgtgccagtc tacaggccta tcagcagcga ctccttcagc aacagatggg gtcccctgtt 60
  cagoccaaco ccatgagoco ccagoagoat atgotoccaa atcaggocca gtocccacac 120
  ctacaaggcc agcagatccc taattctctc tccaatcaag tgcgctctcc ccagcctgtc 180
  cettetecae ggccacagte ccagecece caetecagte ettececaag gatgeageet 240
  cagecttete cacaccacgt tteeceacag acaagtteee cacateetgg actggtagtt 300
  gcccaggcca accccatgga acaagggcat tttgccagcc
  <210> 145
  <211> 630
  <212> DNA
  <213> Homo sapiens
  <400> 145
  tgtaaaaact tgtttttaat tttgtataaa ataaaggtgg tccatgccca cgggggctgt 60
```

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tecteaaaac gggetgagaa ggeeegteag gggeeeaggt cecacagaga ggeetgggat 180
actocccaa ceegagggc agactgggca gtggggagcc cecatcgtgc cecagaggtg 240
gccacagget gaaggaggg cetgaggeac egcageetge aacceecagg getgcagtee 300
actaactttt tacagaataa aaggaacatg gggatgggga aaaaagcacc aggtcaggca 360
gggcccgagg gccccagatc ccaggagggc caggactcag gatgccagca ccaccctagc 420
ageteceaea geteetggea caggaggeeg ceaeggattg geaeaggeeg etgetggeea 480
teacgecaca tttggagaac ttgtcccgac agaggtcage teggaggage teetegtggg 540
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gacagggcac gggaggtctc agccccactt
<210> 146
<211> 521
<212> DNA
<213> Homo sapiens
<400> 146
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ccttgggtct ggagagccat gaagagggaa ggaaaagagg gcaagtcctg aacctaacca 120
atgacetgat ggattgeteg accaagacae agaagtgaag tetgtgtetg tgeaetteee 180
acagactgga gtttttggtg ctgaatagag ccagttgcta aaaaattggg ggtttggtga 240
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<210> 147
<211> 562
<212> DNA
<213> Homo sapiens
<400> 147
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gccgggttgg gacagcgtct tcgctgctgc tggatagtcg tgttttcggg gatcgaggat 120
acteaceaga aacegaaaat geegaaacea ateaatgtee gagttaceae catggatgea 180
gagetggagt ttgcaateca gecaaataca aetggaaaac agetttttga teaggtggta 240
aagactatcg gcctccggga agtgtggtac tttggcctcc actatgtgga taataaagga 300
tttcctacct ggctgaagct ggataagaag gtgtctgccc aggaggtcag gaaggagaat 360
cccctccagt tcaagttccg ggccaaagtt ctaccctgaa gatgtggctg aggagctcat 420
ccaggacatc acccagaaac ttttcttcct tcaagtgaag gaaggaatcc ttagcgatga 480
gatetactge ecceettgar actgeegtge tettggggte etacgettgt geatgeeaag 540
tttggggact accaccaaga ag
<210> 148
<211> 820
<212> DNA
<213> Homo sapiens
<400> 148
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gtctctggga caatctctag ggtcactacc tggaaactcg ttagggtaca actgaatgct 120
gaaaggaaag aacacctgca gaaccggaca gaaattcacc ccggcgatca gctgattqat 180
ctcggtcgac cagaagtcat ggctaaagat gacgaggacg ttgtcaattc cctgggcttt 240
tcgaagtgag tccagcagca gtctgaggta ttcgggccgg ttatgcacct ggaccaccag 300
caccagetee eggggggeee aggtgeeage ettatetaca tteeteaggg tetgateaaa 360
gttcagctgg tacaccaggg accggtaccg cagcgtcagg ttgtccgctc gggctggggg 420
accgccggga ccagggaagc cgccgacacg ttggagaccc tgcggatgcc cacagccaca 480
```

```
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ggggcgaggg cctcgttctt cctttgtcgc ccattgctgc tccagaggac gaagccgcag 600
gcqqccacca cgaqcqtcaq qattaqcacc ttccgtttgt agatgcggaa cctcatggtc 660
tecagggeeg ggagegeage tacagetega gegteggege egeegetagg ageegegget 720
eggettegte teegteetet ceatteagea eeaegggtee eggaaaaage teageesegg 780
tcccaaccgc accctagett cgttacctgc gcctcgcttg
<210> 149
<211> 501
<212> DNA
<213> Homo sapiens
<400> 149
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tgctcttcca gctgcatggc caggcgcaag gccttgatga catctcgcag ggctgagaaa 120
tgcttggctt gctgggccag agcagattcc gctttgttca caaaggtctc caggtcatag 180
totagetget eggteatete agagagetea agecagtetg gteettgetg tatgatetee 240
ttgagctctt ccatagcctt ctcctccagc tccctgatct gagtcatggc ttcgttaaag 300
ctggacatet gggaagacag tteeteetet teettggata aattgeetgg aateagegee 360
ccgttagagc aggcttccat ctcttctgtt tccatttgaa tcaactgctc tccactgggc 420
ccactgtqqq qqctcaqctc cttqaccctg ctqcatatct taaagggtgtt taaaggatat 480
tcacaggage ttatgcctgg t
                                                                   501
<210> 150
<211> 511
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 457, 479
<223> n = A,T,C or G
<400> 150
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qcattctqct ttqactttqc atttqatqaa acaqcttcqa atqaaqttqt ctacaqqttc 120
acagcaaggc cactggtaca gacaatcttt gaaggtggaa aagcaacttg ttttgcatat 180
ggccagacag gaagtggcaa gacacatact atgggcggag acctctctgg gaaagcccag 240
aatgcatcca aagggatcta tgccatggcc ttccgggacg tcttcttctg aagaatcaac 300
cctgctaccg gaagttgggc ctggaagtct atgtgacatt cttcgagatc tacaatggga 360
agetgtttga cetgetcaac aagaaggeca agettgegeg tgetggaaga eggcaagcaa 420
caggtgcaag tggtggggc ttgcaggaac atctggntaa ctctgcttga tgatggcant 480
caagatgatc gacatgggca gcgcctgcag a
<210> 151
<211> 566
<212> DNA
<213> Homo sapiens
<400> 151
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caaatctttt gcgccaagat ctgatgagac gacaggaaga attaagacgc atggaagaac 120
ttcacaatca agaaatgcag aaacgtaaag aaatgcaatt gaggcaagag gaggaacgac 180
gtagaagaga ggaagagatg atgattcgtc aacgtgagat ggaagaacaa atgaggcgcc 240
aaagagagga aagttacagc cgaatgggct acatggatcc acgggaaaga gacatgcgaa 300
tgggtggcgg aggagcaatg aacatgggag atccctatgg ttcaggaggc cagaaatttc 360
cacctctagg aggtggtggt ggcataggtt atgaagctaa tcctggcgtt ccaccagcaa 420
ccatgagtgg ttccatgatg ggaagtgaca tgcgtactga gcgctttggg cagggaggtg 480
```

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cggggcctgt gggtggacag ggtcctagag gaatggggcc tggaactcca gcaggatatg 540
gtagaggag agaagagtac gaaggc
<210> 152
<211> 518
<212> DNA
<213> Homo sapiens
<400> 152
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gatetttget gggaaacage tggaagatgg acgeaecetg tetgaetaea acateeagaa 180
agagtccacc ctgcacctgg tgctccgtct cagaggtggg atgcaaatct tcgtgaagac 240
cctgactggt aagaccatca ccctcgaggt ggagcccagt gacaccatcg agaatgtcaa 300
ggcaaagatc caagataagg aaggcatccc tcctgatcag cagaggttga tctttgctgg 360
gaaacagctg gaagatggac gcaccctgtc tgactacaac atccagaaag agtccactct 420
gcacttggtc ctgcgcttga ggggggtgt ctaagtttcc ccttttaagg tttcaacaaa 480
tttcattgca ctttcctttc aataaagttg ttgcattc
                                                                  518
<210> 153
<211> 542
<212> DNA
<213> Homo sapiens
<400> 153
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tctgctctga gcctccttgt cqcctgcatt taqatggctc ccgcaaagaa qqqtqqcqaq 180
aagaaaaagg gccgttctgc catcaacgaa gtggtaaccc gagaatacac catcaacatt 240
cacaagegea tecatggagt gggetteaag aagegtgeac etegggeact caaagagatt 300
cggaaatttg ccatgaagga gatgggaact ccagatgtgc gcattgacac caggctcaac 360
aaagctgtct gggccaaagg aataaggaat gtgccatacc gaatccgtgt gcggctgtcc 420
agaaaacgta atgaggatga agattcacca aataagctat atactttggt tacctatgta 480
cctgttacca ctttcaaaaa tctacagaca gtcaatgtgg atgagaacta atcgctgatc 540
gt
<210> 154
<211> 411
<212> DNA
<213> Homo sapiens
<400> 154
aattctttat ttaaatcaac aaactcatct tcctcaagcc ccagaccatg gtaggcagcc 60
ctccctctcc atcccctcac cccaccctt agccacagtg aagggaatgg aaaatgagaa 120
gccacgaggg cccctgccag ggaaggctgc cccagatgtg tggtgagcac agtcagtqca 180
gctgtggctg gggcagcagc tgccacaggc tcctccctat aaattaagtt cctgcagcca 240
cagctgtggg agaagcatac ttgtagaagc aaggccagtc cagcatcaga aggcagaggc 300
agcatcagtg actcccagcc atggaatgaa cggaggacac agagctcaga gacagaacag 360
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<210> 155
<211> 421
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 173
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<223> n = A, T, C or G
<400> 155
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actgqttccc taaqaaatcc aaggaqaatc ctcqqaactt ctcqqataac caqctqcaag 120
agggcaagaa cgtgatcggg ttacagatgg gcaccaaccg cggggcgtct cangcaggca 180
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ctcccacgaa tggttaatat atatgtagat atatatttta gcagtgacat tcccaqagag 300
ccccagaget etcaagetee tttetgteag ggtggggggt teaageetgt eetgteacet 360
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                                                                  421
<210> 156
<211> 670
<212> DNA
<213> Homo sapiens
<400> 156
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aactccagcg actgggtaac cactgacatt caggtgaagg tgcgggacac ctacctggat 120
acacaggtgg tgggacagac aggtgtcatc cgcagtgtca cggggggcat gtgctctgtg 180
tacctgaagg acagtgagaa ggttgtcagc atttccagtg agcacctgga gcctatcacc 240
becaceaaga acaacaaggt gaaagtgate etgggegagg ategggaage caegggegte 300
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gtttggtcta
<210> 157
<211> 421
<212> DNA
<213> Homo sapiens
<400> 157
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aagaatcgag ttgaaatcaa tgatgtggag cctgaagttt ttaaggaaat gatgtgcttc 180
atttacacgg ggaaggetee aaacetegae aaaatggetg atgatttget ggeagetget 240
gacaagtatg ccctggagcg cttaaaggtc atgtgtgagg atgccctctg cagtaacctg 300
teegtggaga aegetgeaga aatteteate etggeegaee teeacagtge agateagttg 360
aaaactcagg cagtggattt catcaactat catgcttcgg atgtcttgga gacctcttgg 420
<210> 158
<211> 321
<212> DNA
<213> Homo sapiens
<400> 158
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gttccatgcc aattggtgaa atagaacctc atccggtagt ggagccggag ggacatcttg 120
tcatcaacgg tgatggtgcg atttggagca taccagagct tggtgttctc gccatacagg 180
gcaaagaggt tgtgacaaag aggagagata cggcatgcct gtgcagccct gatgcacagt 240
tectetgetg tgtactetce actgcccage eggaggget ecetgteega eagatagaag 300
atcacttcca cccctggctt g
                                                                  321
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49

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<211> 596
<212> DNA
<213> Homo sapiens
<400> 159
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gggaattcat tttcatcact gggagtgtcc ttagtgtata aaaaccatgc tggtatatgg 180
cttcaagttg taaaaatgaa agtgacttta aaagaaaata ggggatggtc caggatctcc 240
actgataaga ctgtttttaa gtaacttaag gacctttggg tctacaagta tatgtgaaaa 300
aaatgagact tactgggtga ggaaattcat tgtttaaaga tggtcgtgtg tgtgtgtgtg 360
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gvctgtataa gtwctaratg cmtccctggg kgttgatytt ccmagatatt gatgatamcc 540
cttaaaattg taaccygcct ttttcccttt gctytcmatt aaagtctatt cmaaag
<210> 160
<211> 515
<212> DNA
<213> Homo sapiens
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taaggggcgc ctgccagggc cacggccagg aggca
<210> 161
<211> 936
<212> DNA
<213> Homo sapiens
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atccacatca ggagcagaag cacttgactt gtcggtcctg ctgccacggt ttgggcgccc 180
accacgccca cgtccacctc gtcctcccct gccgccacgt cctgggcggc caaggtctcc 240
aaaattgate teeagetgag acgttatate atttgetgge tteeggaaat gatggteeat 300
aaccgaatct tcagcatgag cctcttcact ctttgattta tgaagaacaa atcccttctt 360
ccactgccca tcagcacctt catttggttt tcggatatta aattctactt ttgcccggtc 420
cttattttga atagccttcc actcatccaa agtcatctct tttggaccct cctctttac 480
ctcttcaact tcattctcct tattttcagt gtctgccact ggatgatgtt cttcaccttc 540
aggtgtttcc tcagtcacat ttgattgatc caagtcagtt aattcgtctt tgacagttcc 600
ccagttgtga gatccgctac ctccacgttt gtcctcgtgc ttcaggccag atctatcact 660
tecaetatge etateaaatt caegtttgee aegagaatea aateeatete eteggeeeat 720
tecacgteca eggeeeete gaeetettee aagaeeacea egaeetegaa taggteggte 780
aataatcggt ctatcaactg aaaattcgcc tccttcaccc ttttcttcaa gtggcttttc 840
gaatcttcgt tcacgaggtg gtcgcctttc tggtcttcta tcaattattt tcccttcacc 900
ctgaagttgt tgatcaggtc ttcttccaac tcgtgc
                                                                936
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<210> 162

50

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<211> 950
<212> DNA
<213> Homo sapiens
<400> 162
aageggatgg acctgagtea geegaateet ageecettee ettgggeetg etgtggtget 60
cgacatcagt gacagacgga agcagcagac catcaaggct acgggaggcc cggggcgctt 120
gcgaagatga agtttggctg cctctccttc cggcagcctt atgctggctt tgtcttaaat 180
ggaatcaaga ctgtggagac gcgctggcgt cctctgctga gcagccagcg gaactgtacc 240
ategeegtee acattgetea cagggactgg gaaggegatg cetgteggga getgetggtg 300
gagagactcg ggatgactcc tgctcagatt caggccttgc tcaggaaagg ggaaaagttt 360
ggtcgaggag tgatagcggg actcgttgac attggggaaa ctttgcaatg ccccgaagac 420
ttaactcccg atgaggttgt ggaactagaa aatcaagctg cactgaccaa cctgaagcag 480
aagtacctga ctgtgatttc aaaccccagg tggttactgg agcccatacc taggaaagga 540
ggcaaggatg tattccaggt agacatccca gagcacctga tccctttggg gcatgaagtg 600
tgacaagtgt gggctcctga aaggaatgtt ccrgagaaac cagctaaatc atggcacctt 660
caatttgcca tcgtgacgca gacctgtata aattaggtta aagatgaatt tccactgctt 720
tggagagtec cacceactaa geactgtgea tgtaaacagg tteetttget cagatgaagg 780
aagtaggggg tggggctttc cttgtgtgat gcctccttag gcacacaggc aatgtctcaa 840
qtactttgac cttaggqtag aaggcaaagc tgccagtaaa tgtctcagca ttgctgctaa 900
ttttggtcct gctagtttct ggattgtaca aataaatgtg ttgtagatga
<210> 163
<211> 475
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 301, 317, 331, 458, 464, 470
<223> n = A, T, C or G
<400> 163
tegageggee geeegggeag gtgteggagt ceageaeggg aggegtggte ttgtagttgt 60
teteeggetg eccattgete teccaeteea eggegatgte getgggatag aageetttga 120
ccaggcaggt caggctgacc tggttcttgg tcatctcctc ccgggatggg ggcagggtgt 180
acacctgtgg ttctcggggc tgccctttgg ctttggagat ggttttctcg atgggggctg 240
ggagggcttt gttggagacc ttgcacttgt actccttgcc attcaaccag tcctggtgca 300
ngacggtgag gacgctnacc acacggtacg ngctggtgta ctgctcctcc cgcggctttg 360
tettggcatt atgeacetee acgeegteea egtaceaatt gaacttgace teagggtett 420
cgtggctcac gtccaccacc acgcatgtaa cctcaaanct cggncgcgan cacgc
<210> 164
<211> 476
<212> DNA
<213> Homo sapiens
<400> 164
agcgtggtcg cggccgaggt ctgaggttac atgcgtggtg gtggacgtga gccacgaaga 60
ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa 120
gccgcgggag gagcagtaca acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca 180
ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag ccctcccagc 240
ccccatcgag aaaaccatct ccaaagccaa agggcagccc cgagaaccac aggtgtacac 300
cctgcccca tcccgggagg agatgaccaa gaaccaggtc agcctgacct gcctggtcaa 360
aggettetat eccagegaca tegecegtgg agtgggagag caatgggeag eeggagaaca 420
actacaagac cacgcctccc gtgctggact ccgacacctg ccgggcggcc gctcga
```

<210> 165

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<211> 256
  <212> DNA
  <213> Homo sapiens
  <220>
  <221> misc_feature
  \langle 222 \rangle 10, \overline{3}7, 249
  <223> n = A, T, C or G
  <400> 165
  agcgtggttn cggccgaggt cccaaccaag gctgcancct ggatgccatc aaagtcttct 60
  gcaacatgga gactggtgag acctgcgtgt accccactca gcccagtgtg gcccagaaga 120
  actggtacat cagcaagaac cccaaggaca agaggcatgt ctggttcggc gagagcatga 180
  ccgatggatt ccagttcgag tatggcggcc agggctccga ccctgccgat gtggacctgc 240
  ccgggcggnc gctcga
  <210> 166
. <211> 332
  <212> DNA
  <213> Homo sapiens
  <400> 166
  agcgtggtcg cggccgaggt caagaacccc gcccgcacct gccgtgacct caagatgtgc 60
  cactetgact ggaagagtgg agagtactgg attgacccca accaaggetg caacetggat 120
  gccatcaaag tcttctgcaa catggagact ggtgagacct gcgtgtaccc cactcagccc 180
  agtgtggccc agaagaactg gtacatcagc aagaacccca aggacaagag gcatgtctgg 240
  ttcggcgaga gcatgaccga tggattccag ttcgagtatg gcggccaggg ctccgaccct 300
  geogatgtgg acctgeocgg geggeogete ga
  <210> 167
  <211> 332
  <212> DNA
  <213> Homo sapiens
  <220>
  <221> misc feature
  <222> 77, 109, 136, 184, 198
  <223> n = A, T, C or G
  <400> 167
  tegageggte geeegggeag gtecacateg geagggtegg ageeetggee geeatacteg 60
  aactggaatc catcggncat getctcgccg aaccagacat gectcttgnc cttggggttc 120
  ttgctgatgt accagntctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
  ccantctcca tgttgcanaa gactttgatg gcatccaggt tgcagccttg gttggggtca 240
  atccagtact ctccactctt ccagacagag tggcacatct tgaggtcacg gcaggtgcgg 300
  gcggggttct tgacctcggt cgcgaccacg ct
                                                                      332
  <210> 168
  <211> 276
  <212> DNA
  <213> Homo sapiens
  <220>
  <221> misc feature
  <222> 72, 84
  <223> n = A, T, C or G
 <400> 168
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```
togagoggcc gcccgggcag gtcctcctca gagoggtagc tgttcttatt gccccggcag 60
cctccataga tnaaqttatt qcanqaqttc ctctccacqt caaaqtacca qcqtqgqaag 120
gatgcacggc aaggcccagt gactgcgttg gcggtgcagt attcttcata gttgaacata 180
tegetggagt ggaetteaga atectgeett etgggageae ttgggaeaga ggaateeget 240
gcattcctgc tggtggacct cggccgcgac cacgct
<210> 169
<211> 276
<212> DNA
<213> Homo sapiens
<400> 169
agegtggteg eggeegaggt ceaceageag gaatgeageg gatteetetg teceaagtge 60
tcccagaagg caggattctg aagaccactc cagcgatatg ttcaactatg aagaatactg 120
caccgccaac geagteactg ggccttgccg tgcatccttc ccacgctggt actttgacgt 180
ggagaggaac teetgeaata aetteateta tggaggetge eggggeaata agaacageta 240
ccgctctgag gaggacctgc ccgggcggcc gctcga
                                                                    276
<210> 170
<211> 332
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 294
<223> n = A, T, C or G
<400> 170
tegageggee geeegggeag gtecacateg geagggtegg ageeetggee geeatacteg 60
aactggaatc catcggtcat gctctcgccg aaccagacat gcctcttgtc cttggggttc 120
ttgctgatgt accagttctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
ccagtctcca tgttgcagaa gactttgatg gcatccaggt tgcagccttg gttggggtca 240
atccagtact etccaetett ecagecagaa tggeacatet tgaggteacg geangtgegg 300
gcggggttct tgacctcggc cgcgaccacg ct
<210> 171
<211> 333
<212> DNA
<213> Homo sapiens
<400> 171
agegtggteg eggeegaggt caagaaacce egeegeace tgeegtgace teaagatqtg 60
ccactctggc tggaagagtg gagagtactg gattgacccc aaccaaggct gcaacctgga 120
tgccatcaaa gtcttctgca acatggagac tggtgagacc tgcgtgtacc ccactcagcc 180
cagtgtggcc cagaagaact ggtacatcag caagaacccc aaggacaaga ggcatgtctg 240
geteggegag ageatgaceg atggatteea gttegagtat ggeggeeagg geteegacee 300
tgccgatgtg gacctgcccg ggcggccgct cga
                                                                    333
<210> 172
<211> 527
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 46, \overline{1}25, 140, 148, 220, 229, 291, 388, 456
<223> n = A, T, C or G
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53

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<400> 172
agegtggteg eggeegaggt cetgteagag tggeaetggt agaagnteea ggaaccetga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctgnaatgg ggcccatgan atggttgnct gagagagagc ttcttgtcct acattcggcg 180
ggtatggtct tggcctatgc cttatggggg tggccgttgn gggcggtgng gtccgcctaa 240
aaccatgttc ctcaaagatc atttgttgcc caacactggg ttgctgacca naagtgccag 300
gaagctgaat accatttcca gtgtcatacc cagggtgggt gacgaaaggg gtcttttgaa 360
ctgtggaagg aacatccaag atctctgntc catgaagatt ggggtgtgga agggttacca 420
gttggggaag ctcgctgtct ttttccttcc aatcangggc tcgctcttct gaatattctt 480
cagggcaatg acataaattg tatattcggt tcccggttcc aggccag
<210> 173
<211> 635
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 444, 453, 517, 540, 546, 551, 573, 593
<223> n = A, T, C or G
<400> 173
tegageggee geeegggeag gteeaceaea ceeaatteet tgetggtate atggeageeg 60
ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180
ggaaccqaat atacaattta tqtcattqcc ctqaaqaata atcaqaaqag cqaqccctq 240
attqqaaqqa aaaagacaga cgagcttccc caactggtaa cccttccaca ccccaatctt 300
catggaccag agatettgga tgtteettee acagtteaaa agaceeettt egteaccae 360
cctgggtatg acactggaaa tggtattcag cttcctggca cttctggtca gcaacccagt 420
gttgggcaac aaatgatctt tgangaacat ggntttaggc ggaccacacc ggccacaacg 480
ggcaccccca taaggcatag gccaagaaca tacccgncga atgtaggaca agaagctctn 540
teteanacaa neateteatg ggeeceatte cangacaett etgagtaeat cantteatgg 600
catcctggtg gcactgataa aaacccttac agtta
<210> 174
<211> 572
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 457, 511, 520, 552, 568
<223> n = A, T, C or G
<400> 174
agcgtggtcg cgggcgaggt cctgtcagag tggcactggt agaagttcca ggaaccctga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctggaatgg ggcccatgag atggttgtct gagagagagc ttcttgtcct acattcgqcg 180
ggtatggtct tggcctatgc cttatggggg tggccgttgt gggcggtgtg gtccgcctaa 240
aaccatgttc ctcaaagatc atttgttgcc caacactggg ttgctgacca qaagtqccaq 300
gaagctgaat accatttcca gtgtcatacc cagggtgggt gacgaaaggg gtcttttqaa 360
ctgtggaagg aacatccaag atctctggtc catgaagatt ggggtgtgga agggttacca 420
gttggggaag ctcgtctgtc tttttccttc caatcanggg ctcgctcttc tgattattct 480
tcagggcaat gacataaatt gtatattcgg ntcccgggtn cagccaataa taataaccct 540
ctgtgacacc anggcggggc cgaagganca ct
                                                                  572
```

<210> 175

<213> Homo sapiens

WO 02/06317 PCT/US01/22635

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<211> 372
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 247
<223> n = A, T, C or G
<400> 175
agegtggtcg cggccgaggt cctcaccaga ggtaccacct acaacatcat agtggaggca 60
ctgaaagacc agcagaggca taaggttcgg gaagaggttg ttaccgtggg caactctgtc 120
aacgaaggct tgaaccaacc tacggatgac tcgtgctttg acccctacac agtttcccat 180
tatgccgttg gagatgagtg ggaacgaatg tctgaatcag gctttaaact gttgtgccag 240
tgcttangct ttggaagtgg tcatttcaga tgtgattcat ctagatggtg ccatgacaat 300
ggtgtgaact acaagattgg agagaagtgg gaccgtcagg gagaaaatgg acctgcccgg 360
gcggccgctc ga
<210> 176
<211> 372
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 251
<223> n = A, T, C or G
<400> 176
tegageggee geeegggeag gtecatttte teeetgaegg teceaettet etceaatett 60
gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat gaccacttcc 120
aaagectaag cactggcaca acagtttaaa geetgattea gacattegtt eccaeteate 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caageetteg ntgacagagt tgeccaeggt aacaacetet teeegaacet tatgeetetg 300
ctggtctttc agtgcctcca ctatgatgtt gtaggtggta cctctggtga ggacctcggc 360
cgcgaccacg ct
<210> 177
<211> 269
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 94, 225
<223> n = A, T, C or G
<400> 177
agcgtggccg cggccgaggt ccattggctg gaacggcatc aacttggaag ccaqtgatcg 60
tetcageett ggttetecag etaatggtga tggnggtete agtageatet gteacacgag 120
cccttcttgg tgggctgaca ttctccagag tggtgacaac accctgagct ggtctgcttg 180
tcaaagtgtc cttaagagca tagacactca cttcatattt ggcgnccacc ataagtcctg 240
atacaaccac ggaatgacct gtcaggaac
<210> 178
<211> 529
<212> DNA
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<400> 178
tegageggee geeeggeaq qteeteagae egggttetga gtacacagte agtgtggttg 60
ccttgcacga tgatatggag agccagccc tgattggaac ccagtccaca gctattcctg 120
caccaactga cctgaagttc actcaggtca cacccacaag cctgagcgcc cagtggacac 180
cacccaatgt teageteact ggatategag tgegggtgac ceccaaggag aagaceggac 240
caatgaaaga aatcaacctt gctcctgaca gctcatccgt ggttgtatca ggacttatgg 300
cggccaccaa atatgaagtg agtgtctatg ctcttaagga cactttgaca agcagaccag 360
ctcagggtgt tgtcaccact ctggagaatg tcagcccacc aagaagggct cgtgtgacag 420
atgctactga gaccaccatc accattagct ggagaaccaa gactgagacg atcactggct 480
tocaagttga tgccgttcca gccaatggac ctcggccgcg accacgctt
<210> 179
<211> 454
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 64
<223> n = A, T, C or G
<400> 179
agcgtggtcg cggccgaggt ctggccgaac tgccagtgta cagggaagat gtacatgtta 60
tagntcttct cgaagtcccg ggccagcagc tccacggggt ggtctcctgc ctccaggcgc 120
ttctcattct catggatctt cttcacccgc agcttctgct tctcagtcag aaggttgttg 180
tecteatece teteatacag ggtgaecagg aegttettga gecagteceg eatgegeagg 240
ggqaattcgg tcagctcaga gtccaggcaa ggggggatgt atttgcaagg cccgatgtag 300
tocaagtgga gottgtggco ottottggtg cootcoaagg tgcactttgt ggcaaagaag 360
tggcaggaag agtcgaaggt cttgttgtca ttgctgcaca ccttctcaaa ctcgccaatg 420
ggggctgggc agacctgccc gggcggccgc tcga
<210> 180
<211> 454
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 55, 299, 317, 332, 342, 348
<223> n = A, T, C or G
<400> 180
tcgagcggcc gcccgggcag gtctgcccag ccccattgg cgagtttgag aaggngtgca 60
gcaatgacaa caagacette gactetteet gccacttett tgccacaaag tgcaccetgg 120
agggcaccaa gaagggccac aagctccacc tggactacat cgggccttgc aaatacatcc 180
cccttgcct ggactctgag ctgaccgaat tccccctgcg catgcgggac tggctcaaga 240
acqtcctggt caccctgtat qaqaqqqatq aqqacaacaa ccttctgact qaqaaqcana 300
agctgcgggt gaagaanatc catgagaatg anaagcgcct gnaggcanga gaccaccccq 360
tggagctgct ggcccgggac ttcgagaaga actataacat gtacatcttc cctgtacact 420
ggcagttcgg ccagacctcg gccgcgacca cgct
                                                                   454
<210> 181
<211> 102
<212> DNA
<213> Homo sapiens
<220>
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<221> misc feature
\langle 222 \rangle 8, 47, 60, 67
<223> n = A, T, C or G
<400> 181
agcgtggntg cggacgacgc ccacaaagcc attgtatgta gttttanttc agctgcaaan 60
aataccncca gcatccacct tactaaccag catatgcaga ca
<210> 182
<211> 337
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 169, 195, 253, 314
<223> n = A, T, C or G
<400> 182
tegageggte geeegggeag gtetgggegg atageaeegg geatattttg gaatggatga 60
ggtctggcac cctgagcagc ccagcgagga cttggtctta gttgagcaat ttggctagga 120
ggatagtatg cagcacggtt ctgagtctgt gggatagctg ccatgaagna acctgaagga 180
ggcgctggct ggtangggtt gattacaggg ctgggaacag ctcgtacact tgccattctc 240
tgcatatact ggntagtgag gcgagcctgg cgctcttctt tgcgctgagc taaagctaca 300
tacaatggct ttgnggacct cggccgcgac cacgctt
<210> 183
<211> 374
<212> DNA
<213> Homo sapiens
<400> 183
tegageggee geeegggeag gteeatttte teeetgaegg teceaettet eteeaatett 60
gtagttcaca ccattgtcat gacaccatct agatgaatca catctgaaat gaccacttcc 120
aaagcctaag cactggcaca acagtttaaa gcctgattca gacattcgtt cccactcatc 180
tecaaeggca taatgggaaa etgtgtaggg gteaaageae gagteateeg taggttggtt 240
caageetteg ttgacagaag ttgcccaegg taacaacete ttecegaace ttatgeetet 300
gctggtcttt caagtgcctc cactatgatg ttgtaggtgg cacctctggt gaggacctcg 360
gccgcgacca cgct
<210> 184
<211> 375
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 30, 174, 248, 285, 306, 332, 345, 368
<223> n = A, T, C \text{ or } G
<400> 184
agcgtggttt gcggccgagg tcctcaccan aggtgccacc tacaacatca tagtggaggc 60
actgaaagac cagcagaggc ataaggttcg ggaagaggtt gttaccgtgg gcaactctgt 120
caacgaaggc ttgaaccaac ctacggatga ctcgtgcttt gacccctaca cagnttccca 180
ttatgccgtt ggagatgagt gggaacgaat gtctgaatca ggctttaaac tgttgtgcca 240
gtgcttangc tttggaagtg gtcatttcag atgtgattca tctanatggt gtcatgacaa 300
tggtgngaac tacaagattg gagagaagtg gnaccgtcag ggganaaaat ggacctgccc 360
gggcggcncg ctcga
                                                                    375
```

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<210> 185
<211> 148
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 28, 36, 86
<223> n = A, T, C or G
<400> 185
agcgtggtcg cggccgaggt ctggcttnct gctcangtga ttatcctgaa ccatccaggc 60
caaataagcg ccggctatgc ccctgnattg gattgccaca cggctcacat tgcatgcaag 120
tttgctgagc tgaaggaaaa gattgatc
<210> 186
<211> 397
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 78
<223> n = A, T, C or G
<400> 186
tegageggee geeegggeag gteeaattga aacaaacagt tetgagaeeg ttetteeace 60
actgattaag agtggggngg cgggtattag ggataatatt catttagcct tctgagcttt 120
ctgggcagac ttggtgacct tgccagctcc agcagccttc tggtccactg ctttgatgac 180
acceacegea actgtetgte teatateaeg aacageaaag egacecaaag gtggatagte 240
tgagaagete teaacacaca tgggettgee aggaaccata teaacaatgg geageateae 300
cagacttcaa gaatttaagg gccatcttcc agctttttac cagaacggcg atcaatcttt 360
tccttcagct cagcaaactt gcatgcaatg tgagccg
<210> 187
<211> 584
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 145, 286, 363, 365, 425, 433, 452, 462, 471, 512, 514, 534,
536, 540, 565, 583
<223> n = A, T, C or G
<400> 187
tegageggee geeegggeag gteeagaggg etgtgetgaa gtttgetget geeactggag 60
ccactccaat tgctggccgc ttcactcctg qaaccttcac taaccagatc caggcagect 120
teegggagee aeggettett gtggntaetg acceeaggge tgaceaceag ceteteaegg 180
aggeatetta tgttaaceta cetaceattg egetgtgtaa cacagattet cetetgeget 240
atgtggacat tgccatccca tgcaacaaca agggagctca ctcagngggg tttgatgtgg 300
tggatgctgg ctcgggaagt tctgcgcatg cgtggcacca tttcccgtga acacccatgg 360
gangneatge etgatetgga ettetacaga gateetgaag agattgaaaa agaagaacag 420
gctgnttgct ganaaagcaa gtgaccaagg angaaatttc angggtgaaa nggactgctc 480
ccgctcctga attcactgct actcaacctg angntgcaga ctggtcttga aggngnacan 540
gggccctctg ggcctattta agcancttcg gtcgcgaaca cgnt
```

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<210> 188
<211> 579
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 7, 1\overline{3}6, 486
<223> n = A, T, C or G
<400> 188
agcgtgngtc gcggccgagg tgctgaatag gcacagaggg cacctgtaca ccttcagacc 60
agtotgoaac ctcaggotga gtagcagtga actcaggago gggagcagto cattcaccot 120
gaaattcctc cttggncact gccttctcag cagcagcctg ctcttcttt tcaatctctt 180
caggatetet gtagaagtac agateaggea tgaceteeca tgggtgttea egggaaatgg 240
tgccacgcat gcgcagaact tcccgagcca gcatccacca catcaaaccc actgagtgag 300
ctcccttgtt gttgcatggg atgggcaatg tccacatagc gcagaggaga atctgtgtta 360
cacagegeaa tggtaggtag gttaacataa gatgeeteeg egagaagetg gtggteagee 420
ctggggtcaa gtaaccacaa gaagccgtgg ctcccggaag gctgcctgga tctggttagt 480
qaaggntcca qqaqtqaaqc qqccaacaat tqqaqtqqct tcaqtqqcaa qcaqcaaact 540
tcagcacaag ccctctggac ctgcccggcg gccgctcga
                                                                   579
<210> 189
<211> 374
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 41, 280, 314, 330, 350, 353
<223> n = A, T, C or G
<400> 189
tegageggee geeegggeag gteeatttte teeetgaegg neceaettet etceaatett 60
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aaagcctaag cactggcaca acagtttaaa gcctgattca gacattcgtt cccactcatc 180
tecaaeggea taatgggaaa etgtgtaggg gteaaageae gagteateeg taggttggtt 240
caageetteg ttgacagagt tgeecaeggt aacaaceten teeeegaace ttatgeetet 300
gctgggcttt cagngcctcc actatgatgn tgtaggggg cacctctggn gangacctcg 360
geegegaeca eget
<210> 190
<211> 373
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 247, 304, 306, 332, 337
<223> n = A, T, C or G
<400> 190
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aacgaagget tgaaccaacc tacggatgac tegtgetttg accectacac agttteccat 180
tatgccgttg gagatgagtg ggaacgaatg tctgaatcag gctttaaact gttgtgccag 240
tgcttangct ttggaagtgg gtcatttcag atgtgattca tctagatggt gccatgacaa 300
tggngngaac tacaagattg gagagaagtg gnaccgncag ggagaaaatg gacctgcccg 360
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ggcggccgct cga
                                                                   373
<210> 191
<211> 354
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 218, 299, 306, 326, 333, 337, 341
<223> n = A, T, C or G
<400> 191
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ctggaatcca tcggtcatgc tctcgccgaa ccagacatgc ctcttgtcct tggggttctt 120
getgatgtac cagttettet gggccacact gggctgagtg gggtacacge aggteteace 180
agtctccatg ttgcagaaga ctttgatggc atccaggntg caaccttggt tggggtcaat 240
ccagtactct ccactcttcc agccagagtg gcacatcttg aggtcacggc aggtgcggnc 300
gggggntttt gcggctgccc tctggncttc ggntqtnctc natctgctgg ctca
<210> 192
<211> 587
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 276
<223> n = A, T, C or G
<400> 192
tcgagcggcc gcccgggcag gtctcgcggt cgcactggtg atgctggtcc tgttggtccc 60
cocggocote etggacotec tggcccccet ggtcctccca gcgctggttt cgacttcagc 120
ttcctgcccc agccacctca agagaaggct cacgatggtg gccgctacta ccggggctgat 180
gatgccaatg tggttcgtga ccgtgacctc gaggtggaca ccaccctcaa gagcctgagc 240
cagcagateg agaacateeg gageecagag ggeagnegea agaaceeege eegeacetge 300
cgtgacctca agatgtgcca ctctgactgg aagagtggag agtactggat tgaccccaac 360
caagetgcaa cetggatgce ateaaagtet tetgcaacat ggagaetggt gagaeetgeg 420
tgtaccccac tcagcccagt gtggcccaaa agaactggta catcagcaag aaccccaagg 480
acaagaagca tgtctggttc ggcgagaaca tgaccgatgg attccagttc gagtatggcg 540
ggcagggctc cgaccctgcc gatggggacc ttggccgcga acacgct
<210> 193
<211> 98
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 8, 9, 33, 58, 71, 90
<223> n = A, T, C or G
<400> 193
agcgtggnng cggccgaggt ataaatatcc agnccatatc ctccctccac acgctganag 60
atgaagctgt ncaaagatct cagggtggan aaaaccat
<210> 194
<211> 240
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<212> DNA
<213> Homo sapiens
<400> 194
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gggctccaac ttgcagacgg cctgttgtgg gacagtctct gtaatcgcga aagcaaccat 120
ggaagacctg ggggaaaaca ccatggtttt atccaccctg agatctttga acaacttcat 180
ctctcagcgt gcggagggag gctctggact ggatatttct acctcggccg cgaccacgct 240
<210> 195
<211> 400
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 22, 37, 39, 105, 268, 276, 302, 323, 331, 335, 347, 351,
<223> n = A, T, C or G
<400> 195
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aagctacacc atcacaggtt tacaaccagg cactgactac aaganctacc tgcacacctt 120
gaatgacaat gctcggagct cccctgtggt catcgacgcc tccactgcca ttgatgcacc 180
atecaacetg cqtttcctgg ccaccacace caattccttq ctqqtatcat qqcaqccqcc 240
acgtgccagg attaccggta catcatenag tatganaagc ctgggcctcc tcccagagaa 300
gnaqtecete ggeeegeee tantgteeea naggntaeta ttactgnagee nageaacegge 360
aaccgatate nattttgnca ttggccttca acaataatta
<210> 196
<211> 494
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 19, \overline{8}3, 168, 252, 271, 292, 430
<223> n = A, T, C or G
<400> 196
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tectggaatg gggeecatga gatggttgte tgagagagag ettettgnee tgtettttte 180
cttccaatca ggggctcgct cttctgatta ttcttcaggg caatgacata aattgtatat 240
tegggteeeg gnteeaggee agtaatagta neetetgtga caecagggeg gngeegaggg 300
accacttctc tgggaggaga cccaggcttc tcatacttga tgatgtaacc ggtaatcctg 360
gcacgtggcg gctgccatga taccagcaag gaattggggt gtggtggcca ggaaacgcag 420
gttggatggn gcatcaatgg cagtggaggc cgtcgatgac cacaggggga gctccgacat 480
tgtcattcaa ggtg
                                                                    494
<210> 197
<211> 118
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
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<222> 8, 71, 96
<223> n = A, T, C or G
<400> 197
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taaggagggt neetgeeecc aggagaacat taactnteec cageteggee tetgeegg
<210> 198
<211> 403
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
\langle 222 \rangle 41, \overline{5}3, 98, 195, 350
<223> n = A, T, C or G
<400> 198
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gggagaagct gtggtcagcc caagagggaa tacagagncc cgaaaaaggg gagggcaggt 120
gggctggaac cagacgcagg gccaggcaga aactttctct cctcactgct cagcctggtg 180
gtggctggag ctcanaaatt gggagtgaca caggacacct tcccacagcc attgcggcgg 240
catttcatct ggccaggaca ctggctgtcc acctggcact ggtcccgaca gaagcccgag 300
ctggggaaag ttaatgttca cctgggggca ggaaccctcc ttatcattgn gcagagagca 360
gaaggtggca cagcccgcgc tgcacctcgg ccgcgaccac gct
                                                                    403
<210> 199
<211> 167
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 92, 107
<223> n = A, T, C or G
<400> 199
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ggagcaaggt tgatttettt cattggteeg gnetteteet tgggggneae cegeaetega 120
tatccagtga gctgaacatt gggtggcgtc cactgggcgc tcaggct
<210> 200
<211> 252
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 210, 226, 227, 230, 236
<223> n = A, T, C or G
<400> 200
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gccacgtgcc aggattaccg gctacatcat caagtatgag aagcctgggt ctcctcccag 120
agaagcggtc cctcggcccc gccctggtgt cacagaggct actattactg gcctggaacc 180
gggaaccgaa tatacaattt atgtcattgn cctgaagaat aatcannaan agcgancccc 240
tgattggaag ga
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<210> 201
<211> 91
<212> DNA
<213> Homo sapiens
<400> 201
ttttttttt ttttttttt ttttttt t
<210> 202
<211> 368
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 9, 3\overline{5}4
<223> n = A, T, C or G
<400> 202
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qtccqtqtqc qqqqaqqtaa caaqaaatac cqtqccctqa qqttqqacqt qqqqaatttc 120
tcctggggct cagagtgttg tactcgtaaa acaaggatca tcgatgttgt ctacaatgca 180
tctaataacg agctggttcg taccaagacc ctggtgaaga attgcatcgt gctcatcgac 240
agcacaccgt accgacagtg gtacgagtcc cactatgcgc tgcccctggg ccgcaagaag 300
ggagccaagc tgactcctga ggaagaagag attttaaaca aaaaacgatc taanaaaaaa 360
aaaacaat
<210> 203
<211> 340
<212> DNA
<213> Homo sapiens
<400> 203
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cagtgttggg caacaaatga tctttgagga acatggtttt aggcggacca caccgcccac 120
aacggccacc cccataaggc ataggccaag accatacccg ccgaatgtag gacaagaagc 180
teteteteag acaaccatet catgggeece attecaggae acttetgagt acateattte 240
atgtcatcct gttggcactg atgaagaacc cttacagttc agggttcctg gaacttctac 300
cagtgccact ctgacaggac ctgcccgggc ggccgctcga
<210> 204
<211> 341
<212> DNA
<213> Homo sapiens
<400> 204
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gaactgtaag ggttcttcat cagtgccaac aggatgacat gaaatgatgt actcagaagt 120
gtcctggaat ggggcccatg agatggttgt ctgagagaga gcttcttgtc ctacattcgg 180
cgggtatggt cttggcctat gccttatggg ggtggccgtt gtgggcggtg tggtccgcct 240
aaaaccatgt teetcaaaga teatttgttg eecaacactg ggttgetgae cagaagtgee 300
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                                                                 341
<210> 205
<211> 770
<212> DNA
<213> Homo sapiens
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<220>
<221> misc feature
<222> 529, 591, 623, 626, 629, 630, 656, 702, 709, 712, 717, 743,
746, 749, 759, 762, 766
<223> n = A, T, C or G
<400> 205
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ttggtacgaa ccagctcgtt attagatgca ttgtagacaa catcgatgat ccttgtttta 180
cgagtacaac actctgagcc ccaggagaaa ttccccacgt ccaacctcag ggcacggtat 240
ttettgttac eteceegeac acggactgtg tggatgegge gggggecaag etgacteetg 300
aggaagaaga gattttaaac aaaaaacgat ctaaaaaaat tcagaagaaa tatgatgaaa 360
ggaaaaagaa tgccaaaatc agcagtctcc tggaggagca gttccagcag ggcaagcttc 420
ttgcgtgcat cgcttcaagg ccgggacagt gtgaccgagc agatggctat gtgctagagg 480
gcaaagaagt ggagttctat cttaagaaaa tcagggccca gaatggtgng tcttcaacta 540
atccaaaggg gagtttcaga ccagtgcaat cagcaaaaac attgatactg ntggccaaat 600
ttattggtgc agggcttgca cantangann ggctgggtct tggggcttgg attggnacaa 660
gctttggcag ccttttcttt ggttttgcca aaaacctttt gntgaagang anacctnggg 720
cggacccett aaccgattcc acncenggng gcgttctang gnccencttq
<210> 206
<211> 810
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 574, 621, 625, 636, 668, 673, 704, 728, 743, 767, 772, 786,
789, 807, 809, 810
<223> n = A, T, C or G
<400> 206
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aggetgecaa agaetgttee aataceagea eeagaaceag eeacteetae tgttgeagea 120
cctgcaccaa taaatttggc agcagtatca atgtctctgc tgattgcact ggtctgaaac 180
tecetttgga ttagetgaga cacaccatte tgggeeetga tttteetaag atagaactee 240
aactetttge cetetageae atagecatet geteggteae aetgteeegg cettgaageg 300
atgcacgcaa gaagcttgcc ctgctggaac tgctcctcca ggagactgct gattttggca 360
ttctttttcc tttcatcata tttcttctga atttttttag atcgtttttt gtttaaaatc 420
tettetteet caggagteag ettggeecee geegeateea caeagteegt gtgeggggag 480
gtaacaagaa ataccgtgcc ctgaggttgg acgtggggaa tttctcctgg ggctcagagt 540
ggtgtactcg taaaacaagg atcatcgatg gtgnctacaa tgcatctaat aacgagctgg 600
gteggaceca aagaacetgg ngaanaaatg gategnetea tegacaggae acegtacecg 660
acaggggnac ganteceact atgegettge eectgggeeg caanaaagga aaactgeeeg 720
ggcggccntc gaaagcccaa ttntggaaaa aatccatcac actgggnggc cngtcgagca 780
tgcatntana ggggcccatt cccctnann
                                                                  810
<210> 207
<211> 257
<212> DNA
<213> Homo sapiens
<400> 207
tcgagcggcc gcccgggcag gtccccaacc aaggctgcaa cctggatgcc atcaaagtct 60
tetgeaacat ggagactggt gagacetgeg tgtaceceae teageceagt gtggeecaga 120
agaactggta catcagcaag aaccccaagg acaagaggca tgtctggttc ggcgagagca 180
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64

tgaccgatgg attccagttc gagtatggcg gccagggctc cgaccctgcc gatgtggacc 240 tcggccgcga ccacgct <210> 208 <211> 257 <212> DNA <213> Homo sapiens <400> 208 agcgtggtcg cggccgaggt ccacatcggc agggtcggag ccctggccgc catactcgaa 60 ctggaatcca teggteatge tetegeegaa ecagacatge etettgteet tggggttett 120 gctgatgtac cagttettet gggccacact gggctgagtg gggtacacge aggteteace 180 agtetecatg ttgcagaaga etttgatgge atccaggttg cageettggt tggggacetg 240 cccgggcggc cgctcga <210> 209 <211> 747 <212> DNA <213> Homo sapiens <220> <221> misc feature <222> 453, 538, 540, 542, 546, 554, 556, 598, 659, 670, 679, 689, 693, 711, 723, 724, 731, 747 <223> n = A, T, C or G<400> 209 tegageggee geoegggeag gtecaceaca cecaatteet tgetggtate atggeageeg 60 ccacqtqcca ggattaccqq ctacatcatc aaqtatqaqa aqcctqqqtc tcctcccaqa 120 gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180 ggaaccgaat atacaattta tgtcattgcc ctgaagaata atcagaagag cgagcccctg 240 attggaagga aaaagacaga cgagcttccc caactggtaa cccttccaca ccccaatctt 300 catggaccag agatettgga tgtteettee acagtteaaa agacceettt egteacceae 360 cctgggtatg acactggaaa tggtattcag cttcctggca cttctggtca gcaacccagt 420 gttgggcaac aaatgatctt tgaggaacat ggntttaggc ggaccacacc gcccacaacg 480 gccaccccca taaggcatag gccaagacca tacccgccga atgtaggaca agaagctntn 540 thtcanacac caththatgg gccccattcc aggacacttc tgagtacatc atttatgnca 600 tetgtggcae ttgatgaaaa eeettacagt teagggttet ggaaetttta eeaggeetnt 660 tacaggactn ggccggacnc cttaagccna ttncaccctg gggcgttcta nggtcccact 720 cgnncactgg ngaaaatggc tactgtn 747 <210> 210 <211> 872 <212> DNA <213> Homo sapiens <220> <221> misc feature <222> 165, 174, 181, 256, 260, 269, 271, 277, 286, 289, 294, 298, 300, 301, 303, 308, 311, 321, 325, 328, 329, 333, 338, 342, 346, 349, 351, 357, 359, 364, 366, 379, 385, 395, 396, 397, 407, 408, 410, 414, 415, 429, 431, 434, 435, 440, 443 <223> n = A, T, C or G<221> misc feature <222> 444, 446, 447, 448, 449, 450, 451, 464, 470, 472, 475, 479, 483, 484, 485, 488, 494, 496, 497, 504, 508, 509, 511, 513, 517, 522, 524, 526, 532, 533, 542, 543, 553, 559, 566, 567,

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571, 572, 578, 582, 588, 591, 594, 595, 596, 600, 606
<223> n = A, T, C or G
<221> misc feature
<222> 612, 614, 617, 618, 629, 630, 631, 652, 654, 655, 661, 663,
664, 666, 671, 673, 678, 679, 681, 688, 690, 691, 698, 706,
707, 708, 714, 719, 721, 723, 726, 741, 751, 761, 762, 769,
770, 778, 779, 781, 782, 785, 791, 802, 807, 808, 812
<223> n = A, T, C or G
<221> misc feature
<222> 815, 820, 827, 828, 838, 841, 844, 851, 857, 864, 866, 869,
<223> n = A, T, C or G
<400> 210
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ngagggctaa attccatgaa gtttgtggat ggcctgatga tccacaatcg gagacctgt 240
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ntncttgncc ntccttgggt ngaanatnna atngcctncc cnttcntanc nctactngnt 360
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aaccctatna nttnnattan atnntnnnn nctcacccc ctcntcattn anccnatang 480
ctnnnaantc cttnanncct cccncccnnt ncnctcntac tnantncttc tnncccatta 540
cnnagetett tentttaana taatgnngee nngetetnea tntetaenat ntgnnnaatn 600
cccccnccc cnancqnntt tttgacctnn naacctcctt tcctcttccc tncnnaaatt 660
nennanttee nentteenne nttteggntn nteceatnet tteeannnet teantetane 720
nenetneaac ttattteet nteateett nttetttaca nnececetnn tetaetenne 780
nnttncatta natttgaaac thecaennet anttneeten etetaenntt ttatttneg 840
ntcnctctac ntaatanttt aatnanttnt cn
<210> 211
<211> 517
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 462, 464, 506
<223> n = A, T, C or G
<400> 211
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tatctcatct ttgggttcca caatgctcac gtggtcaggc aggggcttct tagggccaat 180
cttaccagtt gggtcccagg gcagcatgat cttcaccttg atgcccagca caccctgtct 240
gagcaacacg tggcgcacaa gcagtgtcaa cgtagtaagt taacagggtc tccgctgtgg 300
atcatcaggc catccacaaa cttcatggat ttagccctct gtcctcggag tttcccagac 360
accacaacct cgcagccttt ggccccactc tccatgatga accgcagcac accatagcag 420
geocteegea caageaagee etectaagaa tttgtaaege ananactetg etggeaatgg 480
cacacaaacc tctagtggac ctcggncgcg accacgc
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<210> 212
<211> 695
<212> DNA
<213> Homo sapiens
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<220>
<221> misc feature
<222> 432, 476, 522, 547, 621, 624, 647, 679
<223> n = A, T, C or G
<400> 212
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ccagacttga catcatatga atcatactgg ggagaatagt tctgaggacc agtagggcat 120
gattcacaga ttccaggggg gccaggagaa ccaggggacc ctggttgtcc tggaatacca 180
gggtcaccat ttctcccagg aataccagga gggcctggat ctcccttggg gccttgaggt 240
ccttgaccat taggaggcg agtaggagca gttggaggct gtgggcaaac tgcacaacat 300
tctccaaatg gaatttctgg gttggggcag tctaattctt gatccgtcac atattatgtc 360
ategeagaga aeggateetg agteaeagae acatatttgg catggttetg getteeagae 420
atetetatee gneataggae tgaccaagat gggaacatee teetteaaca agettnetgt 480
tgtgccaaaa ataatagtgg gatgaagcag accgagaagt anccagctcc cctttttgca 540
caaagentea teatgtetaa atateagaca tgagaettet ttgggcaaaa aaggagaaaa 600 '
agaaaaagca gttcaaagta nccnccatca agttggttcc ttgcccnttc agcacccggg 660
ccccqttata aaacacctng ggccggaccc ccctt
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<210> 213
<211> 804
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 552, 555, 592, 624, 629, 633, 658, 695, 697, 698, 700, 702,
745, 753, 755, 762, 773, 786, 788, 793, 795
<223> n = A, T, C or G
<400> 213
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gatatttaga catgatgagc tttgtgcaaa aggggagctg gctacttctc gctctgcttc 180
atcccactat tattttggca caacaggaag ctgttgaagg aggatgttcc catcttggtc 240
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caggatccgt tototgcgat gacataatat gtgacgatca agaattagac tgccccaacc 360
cagaaattcc atttggagaa tgttgtgcag tttgcccaca gcctccaact gctcctactc 420
gccctcctaa tggtcaagga cctcaaggcc ccaagggaga tccaggccct cctggtattc 480
ctgggagaaa tggtgaccct ggtattccag gacaaccagg gtcccctggt tctcctggcc 540
cccctggaat cnggngaatc atgccctact ggtcctcaaa ctattctccc anatgattca 600
tatgatgtca agtctgggat agcnagtang ganggactcg caggctattc tggaccanac 660
ctgccggggg ggcgttcgaa agcccgaatc tgcananntn cnttcacact ggcggccgtc 720
gagctgcttt aaaagggcca ttccnccttt agngnggggg antacaatta ctnggcggcg 780
ttttanancg cgngnctggg aaat
<210> 214
<211> 594
<212> DNA
<213> Homo sapiens
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<222> 452, 509, 585
<223> n = A, T, C or G
<400> 214
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gctgatgtac cagttettet gggccacact gggctgagtg gggtacacgc aggteteacc 180
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ggggttettg eggetgeeet etgggeteeg gatgtteteg atetgetgge teaggetett 360
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ccagcgctgg gaggaccagg gggaccaana ggtccaggaa gggcccgggg gggaccaaca 540
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<210> 215
<211> 590
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 8, 9
<223> n = A, T, C or G
<400> 215
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cagcagateg agaacateeg gageecagag ggeageegea agaaceeege eegeacetge 300
cqtqacctca agatqtqcca ctctqactqq aaqaqtqqaq aqtactqqat tqaccccaac 360
caaggctgca acctggatgc catcaaagtc ttctgcaaca tggagactgg tgagacctgc 420
gtgtacccca ctcagcccag tgtggcccag aagaactggt acatcagcaa gaaccccaag 480
gacaagaggc atgtctggtt cggcgagagc atgaccgatg gattccagtt cgagtatggc 540
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<210> 216
<211> 801
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 2, 22, 25, 26, 328, 373, 385, 440, 473, 534, 571, 572, 573,
582, 587, 589, 593, 600, 605, 617, 633, 642, 653, 672, 681,
685, 696, 699, 709, 715, 717, 726, 731, 739, 742, 745, 758,
769, 772, 778, 780, 788, 789, 791, 793, 796
<223> n = A, T, C or G
<400> 216
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acaatggtct ggatggattg aagggacagc ccggtgctcc tggtgtgaag ggtgaacctg 240
gtqcccctgg tqaaaatqga actccaggtc aaacaggagc ccgtgggctt cctggtqaqa 300
gaggaccgtg ttggtgcccc tggcccanac ctcggccgcg accacgctaa gcccgaattt 360
ccaqcacact ggnggccgtt actantggat ccgagctcgg taccaagctt ggcgtaatca 420
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ttaantqaaa tccqccnacc cccqgqqaaa agncggtttg cngtattgqq qcnctttttc 660
cettteeteg gnttaettga nttantggge tttggnegnt tegggttgng geganenggt 720
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aaaacatnng ncnaangggc t
<210> 217
<211> 349
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
\langle 222 \rangle 10, \overline{1}57, 170
<223> n = A, T, C or G
<400> 217
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teacaceagg ageaeeggge tgteeettea atceatneag aceattgtgn cecetaatge 180
etttgaagee aggaagteea ggagtteeag ggaaaceace gageaceetg tggteeaaca 240
actectetet caccaggteg teegggtttt ceagggtgae catetteace ageettgeea 300
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<210> 218
<211> 372
<212> DNA
<213> Homo sapiens
<400> 218
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aaageetaag caetggeaca acagtttaaa geetgattea gacattegtt eecacteate 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caageetteg ttgacagagt tgeccaeggt aacaacetet teeegaacet tatgeetetg 300
ctggtctttc agtgcctcca ctatgatgtt gtaggtggca cctctggtga ggacctcggc 360
cgcgaccacg ct
<210> 219
<211> 374
<212> DNA
<213> Homo sapiens
<400> 219
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aacgaagget tgaaccaacc tacggatgac tegtgetttg acceetacac agttteecat 180
tatgccgttg gagatgagtg ggaacgaatg tctgaatcag gctttaaact gttgtgccag 240
tgcttaggct ttggaagtgg tcatttcaag atgtgattca tctagatggt gccatgacaa 300
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ggccggccgc tcga
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<210> 220
<211> 828
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 8, 9, 557, 571, 587, 588, 601, 642, 643, 647, 654, 664, 681,
688, 698, 719, 720, 725, 734, 738, 743, 744, 757, 765, 773,
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69

778, 780, 782, 783, 793, 798, 805, 809, 822, 827 <223> n = A, T, C or G<400> 220 tegagegnne geeegggeag gteeagtagt geetteggga etgggtteae eeceaggtet 60 geggeagttg teacagegee ageecegetg geetecaaag catgtgeagg ageaaatgge 120 accgagatat teettetgee actgttetee täegtggtat gtetteeeat categtaaca 180 cgttgcctca tgagggtcac acttgaattc tccttttccg ttcccaagac atgtgcagct 240 catttggctg gctctatagt ttggggaaag tttgttgaaa ctgtgccact gacctttact 300 tecteettet etactggage titegtacet tecaettetg etgtiggtaa aatggtggat 360 cttctatcaa tttcattgac agtacccact tctcccaaac atccagggaa atagtgattt 420 cagagcgatt aggagaacca aattatgggg cagaaataag gggcttttcc acaggttttc 480 ctttggagga agatttcagt ggtgacttta aaagaatact caacagtgtc ttcatcccca 540 tagcaaaaga agaaacngta aatgatggaa ngcttctgga gatgccnnca tttaagggac 600 neceagaact teaceateta caggacetae tteagtttae annaagneae atantetgae 660 tcanaaagga cccaagtagc nccatggnca gcactttnag cctttcccct ggggaaaann 720 ttacnttett aaaneetngg eenngaeeee ettaagneea aattntggaa aantteentn 780 828 cnnctggggg gengttenac atgentttna agggeceaat tneecent <210> 221 <211> 476 <212> DNA <213> Homo sapiens <400> 221 tcgagcggcc gcccgggcag gtgtcggagt ccagcacggg aggcgtggtc ttgtagttgt 60 tctccqqctq cccattqctc tcccactcca cqqcqatqtc qctqqqataq aaqcctttqa 120 ccaggcaggt caggctgacc tggttcttgg tcatctcctc ccgggatggg ggcagggtgt 180 acacctgtgg ttctcggggc tgccctttgg ctttggagat ggttttctcg atgggggctg 240 ggagggettt gttggagace ttgeacttgt acteettgee atteagecag teetggtgea 300 ggacggtgag gacgctgacc acacggtacg tgctgttgta ctgctcctcc cgcggctttg 360 tettggcatt atgcacetee acgeegteea egtaceagtt gaacttgace teagggtett 420 cgtggctcac gtccaccacc acgcatgtaa cctcagacct cggccgcgac cacgct <210> 222 <211> 477 <212> DNA <213> Homo sapiens <400> 222 agcgtggtcg cggccgaggt ctgaggttac atgcgtggtg gtggacgtga gccacgaaga 60 ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa 120 gccgcgggag gagcagtaca acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca 180 ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag ccctcccagc 240 ccccatcgag aaaaccatct ccaaagccaa agggcaagcc ccgagaacca caggtgtaca 300 ccctgcccc atcccgggag gagatgacca agaaccaggt cagcctgacc tqcctggtca 360 aaggetteta teecagegae ategeegtgg agtgggagag caatgggeag eeggagaaca 420 actacaagac cacqcctccc gtqctggact ccgacacctg cccqqqcqqc cqctcqa <210> 223 <211> 361 <212> DNA <213> Homo sapiens <400> 223 tcgagcggcc gcccgggcag gttgaatggc tcctcgctga ccaccccggt gctggtggtg 60 ggtacagagc teegatgggt gaaaccattg acatagagac tgteeetgte cagggtgtag 120 gggcccagct cagtgatgcc gtgggtcagc tggctcagct tccagtacag ccgctctctg 180

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<210> 224
<211> 361
<212> DNA
<213> Homo sapiens
<400> 224
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gtgtcagctc tctgtactct ggttgcagac tgaccttgct caggcctgag aaggatgggg 120
cagccaccag agtggatgct gtctgcaccc atcgtcctga ccccaaaagc cctggactgg 180
acagagagcg gctgtactgg aagctgagcc agctgaccca cggcatcact gagctgggcc 240
cctacaccct ggacagggac agtctctatg tcaatggttt cacccatcgg agctctgtac 300
ccaccaccag caccggggtg gtcagcgagg agccattcaa cctgcccggg cggccgctcg 360
                                                                  361
<210> 225
<211> 766
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 574, 610, 631, 643, 657, 660, 666, 688, 712, 735, 747
<223> n = A, T, C or G
<400> 225
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actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctggaatgg ggcccatgag atggttgtct gagagagagc ttcttgtcct acattcggcg 180
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gaagetgaat accattteea gtgteataee eagggtgggt gaegaaaggg gtettttgaa 360
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gttggggaag ctcgtctgtc tttttccttc caatcagggg ctcgctcttc tgattattct 480
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<211> 364
<212> DNA
<213> Homo sapiens
<400> 226
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cgagaatgca gagtttcctc tgtgatatca agcacttcag ggttgtagat gctgccattg 240
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agogtggctt cgctqqctcc cactttqtct ccagtcttga tcagacctcg gccqcgacca 360
cgct
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<210> 227
 <211> 275
 <212> DNA
 <213> Homo sapiens
 <400> 227
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 atgeccaceg tgeccageae etgaacteet ggggggaceg teagtettee tettecceeg 240
 cateceett ecaaacetge eeggeggee geteg
 <210> 228
 <211> 275
 <212> DNA
 <213> Homo sapiens
 <400> 228
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 gctcaactct cttgtccacc ttggtgttgc tgggcttgtg atctacgttg caggtgtagg 180
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 <210> 229
 <211> 40
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc feature
 <222> 1, 4, 5, 13, 15, 17, 29
 <223> n = A, T, C or G
 <400> 229
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 <210> 230
 <211> 208
 <212> DNA
 <213> Homo sapiens
 <400> 230
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 gaagegeaga tetgttttaa agteetgage aatttetege accagaeget ggaagggaag 120
 tttgcgaatc agaagttcag tggacttctg ataacgtcta atttcacgga gcgccacagt 180
 accaggacet geeegggegg cegetega
 <210> 231
 <211> 208
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <222> 33
 <223> n = A, T, C or G
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<400> 231
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tcaggacttt aaaacagatc tgcgcttcca gagcgcagct atcggtgctt tgcaggaggc 180
aagtgaggac ctcggccgcg accacgct
<210> 232
<211> 332
<212> DNA
<213> Homo sapiens
<400> 232
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ttgctgatgt accagttctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
ccagteteca tgttgcagaa gactttgatg gcatecaggt tgcagcettg gttggggtca 240
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<210> 233
<211> 415
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 6, 15, 19, 21
<223> n = A, T, C or G
<400> 233
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<210> 234
<211> 776
<212> DNA
<213> Homo sapiens
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<221> misc_feature
<222> 505, 550, 574, 601, 604, 608, 612, 649, 656, 657, 680, 711,
750, 776
<223> n = A, T, C or G
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ggaccaggac caacaaaaac taaaactgca ggtccagatc aaacagaaat gactattgaa 420
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ncangtonag gnggacotac togagocotg aggatggaat cottgactnt toottnnoot 660
gatggggaaa aaaaaccttn aaaacttgaa ggacctgccc gggcggccgt ncaaaaccca 720
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<211> 805
<212> DNA
<213> Homo sapiens
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<222> 637, 684, 705, 724, 733, 756, 778, 793, 796, 804
<223> n = A, T, C or G
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ttgcccctgt gggctttccc aagcaatttt gatggaatcg gcatccacat cagtgaatgc 180
cagteettta gggegateaa tgttggttae tgeagtetga accagagget gaetetetee 240
gcttggattc tgagcataga cactaaccac atactccact gtgggctgca agccttcaat 300
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aatgctgttg tcctgaacat cggtcacttg catctgggat ggtttgtcaa tttctgttcg 480
gtaattaatg gaaattggct tgctgcttgc ggggcttgtc tccacggcca gtgacagcat 540
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ccaggcacaa gtgaactcct gacagggcta tttcctnctg ttctccgtaa gtgatcctgt 660
aatateteae tgggacagea ggangeatte caaaaetteg ggegngacee eetaageega 720
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cctataggga gtntantaca attng
<210> 236
<211> 262
<212> DNA
<213> Homo sapiens
<400> 236
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attgtctccc atttttttgg cttttgaggg ggttcagttt gggttgcttg tctgtttccg 180
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<211> 372
<212> DNA
<213> Homo sapiens
<400> 237
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aacgaaggct tgaaccaacc tacggatgac tcgtgctttg acccctacac aqtttcccat 180
tatgccqttq qaqatqaqtq qqaacqaatq tctqaatcaq qctttaaact qttqtqccaq 240
tgcttaggct ttggaagtgg tcatttcaga tgtgattcat ctagatggtg ccatgacaat 300
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<210> 238
<211> 372
<212> DNA
<213> Homo sapiens
<400> 238
tcgagcgcc gcccggcag gtccattttc tccctgacgg tcccacttct ctccaatctt 60
gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat gaccacttcc 120
aaagcctaag cactggcaca acagtttaaa gcctgattca gacattcgtt cccactcatc 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caageetteg ttgacagagt tgeccaeggt aacaacetet teeegaacet tatgeetetg 300
ctggtctttc agtgcctcca ctatgatgtt gtaggtggca cctctggtga ggacctcggc 360
cgcgaccacg ct
<210> 239
<211> 720
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 478, 557, 563, 566, 620, 660, 663, 672, 673, 684, 693, 695
<223> n = A, T, C \text{ or } G
<400> 239
tegageggee geeegggeag gteeaceata agteetgata caaceaegga tgagetgtea 60
ggagcaaggt tgatttettt cattggteeg gtetteteet tgggggteae eegeactega 120
tatecagtga getgaacatt gggtggtgte caetgggege teaggettgt gggtgtgace 180
tgagtgaact tcaggtcagt tggtgcagga atagtggtta ctgcagtctg aaccagaggc 240
tgactctctc cgcttggatt ctgagcatag acactaacca catactccac tgtgggctgc 300
aagccttcaa tagtcatttc tgtttgatct ggacctgcag ttttagtttt tgttggtcct 360
ggtccatttt tgggagtggt ggttactctg taaccagtaa caggggaact tgaaggcagc 420
cacttgacac taatgctgtt gtcctgaaca tcggtcactt gcatctggga tggtttgnca 480
atttctgttc ggtaattaat ggaaattggc ttgctgcttg cggggctgtc tccacggcca 540
gtgacagcat acacagngat ggnatnatca actccaagtt taaggccctg atggtaactt 600
taaacttgct cccagccagn gaacttccgg acagggtatt tcttctggtt ttccgaaagn 660
gancetggaa tnnteteett ggancagaag ganenteeaa aacttgggee ggaaceeett 720
<210> 240
<211> 691
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 564, 582, 640, 651, 666, 669, 690
<223> n = A, T, C or G
<400> 240
agegtggteg eggeegaggt cetgteagag tggeactggt agaagtteea ggaaceetga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctggaatgg ggcccatgag atggttgtct gagagagagc ttcttgtcct acattcggcg 180
ggtatggtct tggcctatgc cttatggggg tggccgttgt gggcggtgtg gtccgcctaa 240
aaccatgttc ctcaaagatc atttgttgcc caacactggg ttgctgacca gaagtgccag 300
gaagetgaat accatttcca gtgtcatacc cagggtgggt gacgaaaggg gtcttttgaa 360
ctgtggaagg aacatccaag atctctggtc catgaagatt ggggtgtgga agggttacca 420
gttggggaag ctcgtctgtc tttttccttc caatcagggg ctcgctcttc tgattattct 480
```

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tcagggcaat gacataaatt gtatattcgg ttcccggttc caggccagta atagtagcct 540
cttgtgacac caggcggggc ccanggacca cttctctggg angagaccca gcttctcata 600
cttgatgatg taacceggta atcctgcacg tggcggctgn catgatacca ncaaggaatt 660
gggtgnggng gacctgcccg gcggccctcn a
<210> 241
<211> 808
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 680, 715, 721, 728, 735, 749, 757, 762, 772, 776, 779, 781,
792, 796, 800, 808
<223> n = A, T, C or G
<400> 241
agcgtggtcg cggccgaggt ctgggatgct cctgctgtca cagtgagata ttacaggatc 60
acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
totacagota coatcagogg cottaaacot ggagttgatt ataccatcac tgtgtatgot 180
gtcactggcc gtggagacag ccccgcaagc agcaagccaa tttccattaa ttaccgaaca 240
gaaattqaca aaccatccca qatqcaaqtq accqatqttc aqqacaacaq cattaqtqtc 300
aagtggctgc cttcaagttc ccctgttact ggttacagag taaccaccac tcccaaaaat 360
ggaccaggac caacaaaaac taaaactgca ggtccagatc aaacagaaat gactattgaa 420
ggcttgcagc ccacagtgga gtatgtggtt agtgtctatg ctcagaatcc aagcggagag 480
agtcagcctc tggttcagac tgcagtaacc actattcctg caccaactga cctgaagttc 540
actcaggtca cacccacaag cctgagccgc cagtggacac cacccaatgt tcactcactg 600
gatatcgagt gcgggtgacc cccaaggaga agacccggac ccatgaaaga aatcaacctt 660
gctcctgaca gctcatccgn gggtgtatca ggacttatgg gggactgccc cggcnggccg 720
ntegaaaneg aattntgaaa ttteettene aetgggngge gnttegaget tnettntana 780
nggcccaatt cncctntagn gggtcgtn
<210> 242
<211> 26
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 22
<223> n = A, T, C or G
<400> 242
                                                                   26
agcgtggtcg cggccgaggt cnagga
<210> 243
<211> 697
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 496, 541, 624, 662, 679, 688
<223> n = A, T, C or G
<400> 243
tcgagcggcc gcccgggcag gtccaccaca cccaattcct tgctggtatc atggcagccg 60
ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
```

76

gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180 ggaaccgaat atacaattta tgtcattgcc ctgaagaata atcagaagag cgagcccctg 240 attggaagga aaaagacaga cqaqcttccc caactggtaa cccttccaca ccccaatctt 300 catggaccag agatettgga tgtteettee acagtteaaa agacceettt egteacceae 360 cctgggtatg acactggaaa tggtattcag cttcctggca cttctggtca gcaacccagt 420 gttgggcaac aaatgatett tgaggaacat ggttttagge ggaccacace geecacaaeg 480 ggcaccccca taaggnatag gccaagacca taccccgccg aatgtaggac aagaagctct 540 nteteaacaa ceateteatg ggeeceatte caggacaett etgagtaeat cattteatgt 600 catcctggtg ggcacttgat gaanaaccct tacagttcag ggttcctgga acttctacca 660 gngccacttc tgacagganc ttgggcgnga ccaccct <210> 244 <211> 373 <212> DNA <213> Homo sapiens <400> 244 agogtggtcg cggccgaggt ccattttctc cctgacggtc ccacttctct ccaatcttgt 60 agttcacacc attgtcatgg caccatctag atgaatcaca tctgaaatga ccacttccaa 120 agectaagea etggeacaac agtttaaage etgatteaga eattegttee eacteatete 180 caacggcata atgggaaact gtgtaggggt caaagcacga qtcatccgta ggttggttca 240 agecttegtt gaeagagttg ceeaeggtaa caacetette eegaacetta tgeetetget 300 ggtctttcag tgcctccact atgatgttgt aggtggcacc tctggtgagg acctgcccgg 360 gcggcccgct cga <210> 245 <211> 307 <212> DNA <213> Homo sapiens <400> 245 agegtggteg eggeegaggt gtgeeceaga ceaggaatte ggettegaeg ttggeeetgt 60 etgetteetg taaacteect ceateceaac etggeteet eccacecaac caacttteec 120 cccaacccgg aaacagacaa gcaacccaaa ctgaaccccc tcaaaagcca aaaaaatggg 180 agacaatttc acatggactt tggaaaatat tttttcctt tgcattcatc tctcaaactt 240 agtttttatc tttgaccaac cgaacatgac caaaaaccaa aagtgacctg cccgggcggc 300 cgctcga <210> 246 <211> 372 <212> DNA <213> Homo sapiens <400> 246 tegageggee geeegggeag gteeteacea gaggtgeeae etacaacate atagtggagg 60 cactgaaaga ccagcagagg cataaggttc gggaagaggt tgttaccgtg ggcaactctg 120 tcaacgaagg cttgaaccaa cctacggatg actcgtgctt tgacccctac acagtttccc 180 attatgccgt tggagatgag tgggaacgaa tgtctgaatc aggctttaaa ctgttgtgcc 240 agtgcttagg ctttggaagt ggtcatttca gatgtgattc atctagatgg tgccatgaca 300 atggtgtgaa ctacaagatt ggagagaagt gggaccgtca gggagaaaat ggacctcggc 360 cgcqaccacq ct 372 <210> 247 <211> 348 <212> DNA <213> Homo sapiens <220>

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<221> misc feature
<222> 284, 297, 299, 322, 325, 338, 342, 345
\langle 223 \rangle n = A, T, C or G
<400> 247
tcgagcggcc gcccgggcag gtaccggggt ggtcagcgag gagccattca cactgaactt 60
caccatcaac aacctgcggt atgaggagaa catgcagcac cctggctcca ggaagttcaa 120
caccacggag agggtccttc agggcctgct caggtccctg ttcaagagca ccagtgttgg 180
ccctctgtac tctggctgca gactgacttt gctcagacct gagaaacatg gggcagccac 240
tggagtggac gccatctgca ccctccgcct tgatcccact ggtnctggac tggacanana 300
geggetatac ttgggagetg ancenaacet ttggeggnga encenett
<210> 248
<211> 304
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 125
<223> n = A, T, C or G
gaggactggc tcagctccca gtatagccgc tctctgtcca gtccaggacc agtgggatca 60
aggeggaggg tgcagatggc gtccactcca gtggctgccc catgtttctc aagtctgagc 120
aaagncagtc tgcagccaga gtacagaggg ccaacactgg tgctcttgaa cagggacctg 180
agcaggccct gaaggaccct ctccgtggtg ttgaacttcc tggagccagg gtgctgcatg 240
ttctcctcat accgcaggtt gttgatggtg aagttcagtg tgaatggctc ctcgctgacc 300
accc
<210> 249
<211> 400
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 308, 310, 312, 320, 331, 336, 383, 392, 396
<223> n = A, T, C or G
<400> 249
agcgtggtcg cggccgaggt ccaccacacc caattccttg ctggtatcat ggcagccgcc 60
acgtgccagg attaccggct acatcatcaa gtatgagaag cctgggtctc ctcccagaga 120
agtggtccct cggccccgcc ctggtgtcac agaggctact attactggcc tggaaccggg 180
aaccgaatat acaatttatg tcattgccct gaagaataat cagaagagcg agcccctgat 240
tggaaggaaa aagacagacg agcttcccca actggtaacc cttccacacc ccaatcttca 300
tggaccanan ancttggatn gtcctttcac nggttnaaaa aacccttttc gccccccac 360
cttggggatt aaccttggga aanggggatt tnaccnttcc
                                                                    400
<210> 250
<211> 400
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 338, 357, 361, 369, 388, 394
<223> n = A, T, C or G
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<400> 250
tegageggee geeegggeag gteetgteag agtggeaetg gtagaagtte caggaaceet 60
qaactqtaaq qqttcttcat caqtqccaac aqqatqacat qaaatqatqt actcaqaaqt 120
gtcctggaat ggggcccatg agatggttgt ctgagagaga gcttcttgtc ctacattcqq 180
cgggtatggt cttggcctat gccttatggg ggtggccgtt gtgggcggtg tgqtccgcct 240
aaaaccatgt tootcaaaga toatttgttg cocaacactg ggttgctgac cagaagtgcc 300
aggaagetga ataccattte cagtgteata eccagggngg gtgaccaaag ggggtenttt 360
ngacctggng aaaggaacca tccaaaanct ctgncccatg
                                                                   400
<210> 251
<211> 514
<212> .DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 8, 107, 312, 338, 351, 352, 357, 363, 366, 373, 380, 405,
421, 444, 508
<223> n = A, T, C or G
<400> 251
agcgtggncg cggccgaggt ctgaggatgt aaactcttcc caggggaagg ctgaagtgct 60
gaccatggtg ctactgggtc cttctgagtc agatatgtga ctgatgngaa ctgaagtagg 120
tactgtagat ggtgaagtct gggtgtccct aaatgctgca tctccagagc cttccatcat 180
taccgtttct tcttttgcta tgggatgaga cactgttgag tattctctaa agtcaccact 240
gaaatettee teeaaaggaa aacetgtgga aaageeeett atttetgeee cataatttgg 300
ttctcctaat cnctctgaaa tcactatttc cctggaangt ttgggaaaaa nngggcnacc 360
tgncantgga aantggatan aaagatccca ccattttacc caacnagcag aaagtgggaa 420
nggtaccgaa aagctccaag taanaaaaag gagggaagta aaggtcaagt gggcaccagt 480
ttcaaacaaa actttcccca aactatanaa ccca
<210> 252
<211> 501
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 20, 21, 25, 44, 343, 347, 356, 362, 387, 391, 398, 409, 428,
430, 453, 494
<223> n = A, T, C or G
<400> 252
aageggeege cegggeaggn neagnagtge ettegggaet gggnteacce ceaggtetge 60
ggcagttgtc acagegecag eccegetgge etccaaagea tgtgcaggag caaatggcae 120
cgagatattc cttctgccac tgttctccta cgtggtatgt cttcccatca tcgtaacacg 180
ttgcctcatg agggtcacac ttgaattctc cttttccgtt cccaagacat gtgcagctca 240
tttggctggc tctatagttt ggggaaagtt tgttgaaact gtgccactqa cctttacttc 300
cteettetet aetggagett teegtaeett ceaettetge tgntggnaaa aagggnggaa 360
cntcttatca atttcattgg acagtanccc nctttctncc caaaacatnc aagggaaaat 420
attgattncn agagcggatt aaggaacaac ccnaattatg ggggccagaa ataaaggggg 480
cttttccaca ggtnttttcc t
                                                                   501
<210> 253
<211> 226
<212> DNA
<213> Homo sapiens
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<400> 253
tcqaqcqgcc qcccggqcaq qtctqcaqqc tattqtaaqt gttctgaqca catatgagat 60
aacctgggcc aagctatgat gttcgatacg ttaggtgtat taaatgcact tttgactgcc 120
atctcagtgg atgacagcct tctcactgac agcagagatc ttcctcactg tgccagtggg 180
caggagaaag agcatgctgc gactggacct cggccgcgac cacgct
<210> 254
<211> 226
<212> DNA
<213> Homo sapiens
<400> 254
agcgtggtcg cggccgaggt ccagtcgcag catgctcttt ctcctgccca ctggcacagt 60
gaggaagatc tctgctgtca gtgagaaggc tgtcatccac tgagatggca gtcaaaagtg 120
catttaatac acctaacgta tcgaacatca tagcttggcc caggttatct catatgtgct 180
cagaacactt acaatagect geagacetge eegggeggee getega
<210> 255
<211> 427
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 327, 403
<223> n = A, T, C or G
<400> 255
cgagcggccg cccgggcagg tccagactcc aatccagaga accaccaagc cagatgtcag 60
aagctacacc atcacaggtt tacaaccagg cactgactac aagatctacc tgtacacctt 120
gaatgacaat gctcggagct cccctgtggt catcgacgcc tccactgcca ttgatgcacc 180
atccaacctg cgtttcctgg ccaccacac caattccttg ctggtatcat ggcagccgcc 240
acgtgccagg attaccggct acatcatcaa gtatgagaag cctgggtctc ctcccagaga 300
agtggtccct cggccccgcc ctggtgncac agaagctact attactggcc tggaaccggg 360
aaccgaatat acaatttatg tcattgccct qaagaataat canaagagcg agcccctgat 420
tggaagg
<210> 256
<211> 535
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 347, 456, 475
<223> n = A, T, C or G
<400> 256
agegtggteg eggeegaggt cetgteagag tggeaetggt agaagtteea ggaaceetga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctggaatgg ggcccatgag atggttgtct gagagagagc ttcttgtcct gtcttttcc 180
ttccaatcag gggctcgctc ttctgattat tcttcagggc aatgacataa attgtatatt 240
cggttcccgg ttccaggcca gtaatagtag cctctgtgac accagggcgg ggccgaggga 300
ccacttctct gggaggagac ccaggcttct catacttgat gatgtanccg gtaatcctgg 360
caccgtggcg gctgccatga taccagcaag gaattgggtg tggtggccaa gaaacgcagg 420
ttggatggtg catcaatggc agtggaggcg tcgatnacca caggggagct ccgancattg 480
tcattcaagg tggacaggta gaatcttgta atcaggtgcc tggtttgtaa acctg
                                                                  535
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80

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<210> 257
<211> 544
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 495, 511
<223> n = A, T, C or G
<400> 257
tegageggee geeegggeag gtttegtgae egtgaeeteg aggtggaeae cacceteaag 60
agcctgagcc agcagatcga gaacatccgg agcccagagg gcagccgcaa gaaccccgcc 120
cgcacctgcc gtgacctcaa gatgtgccac tctgactgga agagtggaga gtactggatt 180
gaccccaacc aaggetgcaa cetggatgcc atcaaagtet tetgcaacat ggagactggt 240
gagacetgeg tgtaceccae teageceagt gtggeecaga agaactggta cateageaag 300
aaccccaagg acaagaagca tgtctggttc ggcgaaagca tgaccgatgg attccagttc 360
gagtatggcg gccagggctc cgaccctgcc gatgtggacc tcggccgcga ccacgctaag 420
cccgaattcc agcacactgg cggccgttac tagtgggatc cgagcttcgg taccaagctt 480
ggcgtaatca tgggncatag ctgtttcctg ngtgaaaatg gtattccgct tcacaatttc 540
ccac
<210> 258
<211> 418
<212> DNA
<213> Homo sapiens
<400> 258
agegtggteg eggeegaggt ceacategge agggteggag ecetggeege catactegaa 60
ctggaatcca tcggtcatgc tctcgccgaa ccagacatgc ctcttgtcct tggggttctt 120
gctgatgtac cagttcttct gggccacact gggctgagtg gggtacacgc aggtctcacc 180
agtetecatg ttgcagaaga etttgatgge atecaggttg cageettggt tggggteaat 240
ccagtactct ccactcttcc agtcagagtg gcacatcttg aggtcacggc aggtgcgggc 300
ggggttettg eggetgeect etgggeteeg gatgtteteg atetgetgge teaagetett 360
gaagggtggt gtccacctcg aggtcacggt cacgaaacct gcccgggcgg ccgctcga
<210> 259
<211> 377
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 320, 326, 342, 352
<223> n = A, T, C or G
<400> 259
agogtggtcg cggccgaggt caagaacccc qcccgcacct qccgtgacct caagatgtgc 60
cactetgact ggaagagtgg agagtactgg attgacccca accaaggetg caacetggat 120
gccatcaaag tcttctgcaa catggagact ggtgagacct gcgtgtaccc cactcagccc 180
agtgtggccc agaagaactg gtacatcagc aagaacccca aggacaagag gcatgtctgg 240
ttcggcgaga gcatgaccga tggattccag ttcgagtatg gcggccaggg ctccgaccct 300
gccgatgtgg acctgcccgn gccggnccgc tcgaaaagcc cnaatttcca gncacacttg 360
gccggccgtt actactg
<210> 260
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<211> 332

PCT/US01/22635 WO 02/06317

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<212> DNA
<213> Homo sapiens
<400> 260
tegageggee geeegggeag gtecacateg geagggtegg ageeetggee gecatacteg 60
aactggaatc categgteat getetegeeg aaccagacat geetettgte ettggggtte 120
ttgctgatgt accagttctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
ccagtctcca tgttgcagaa gactttgatg gcatccaggt tgcagccttg gttggggtca 240
atccagtact ctccactctt ccagtcagag tggcacatct tgaggtcacg gcaggtgcgg 300
geggggttet tgacetegge egegaeeaeg et
                                                                332
<210> 261
<211> 94
<212> DNA
<213> Homo sapiens
<400> 261
ttttttttt ttttttttt ttttttttt
<210> 262
<211> 650
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 412, 582, 612, 641, 646
<223> n = A, T, C or G
<400> 262
agegtggteg eggeegaggt etggeattee ttegaettet etceageega getteecaga 60
acatcacata tcactgcaaa aatagcattg catacatgga tcaggccagt ggaaatgtaa 120
agaaggccct gaagctgatg gggtcaaatg aaggtgaatt caaggctgaa ggaaatagca 180
aattcaccta cacagttctg gaggatggtt gcacgaaaca cactggggaa tggagcaaaa 240
cagtetttga atategaaca egeaaggetg tgagactace tattgtagat attgcaccet 300
atgacattgg tggtcctgat caagaatttg gtgtggacgt tggccctgtt tgctttttat 360
aaaccaaact ctatctgaaa tcccaacaaa aaaaatttaa ctccatatgt gntcctcttg 420
ttctaatctt ggcaaccagt gcaagtgacc gacaaaattc cagttattta tttccaaaat 480
gtttggaaac agtataattt gacaaagaaa aaaggatact tctctttttt tggctggtcc 540
accaaataca attcaaaagg ctttttggtt ttatttttt anccaattcc aatttcaaaa 600
tgtctcaatg gngcttataa taaaataaac tttcaccctt nttttntgat
                                                                650
<210> 263
<211> 573
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 453, 458, 544
\langle 223 \rangle n = A,T,C or G
<400> 263
agcgtggtcg cggccgaggt ctgggatgct cctgctgtca cagtgagata ttacaggatc 60
acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
tctacagcta ccatcagcgg ccttaaacct ggagttgatt ataccatcac tgtgtatgct 180
qtcactggcc qtqgaqacag ccccqcaagc aqcaagccaa tttccattaa ttaccqaaca 240
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gaaattgaca aaccatccca gatgcaagtg accgatgttc aggacaacag cattagtgtc 300
aagtggctgc cttcaagttc ccctgttact ggttacagaa gtaaccacca ctcccaaaaa 360
tggaccagga ccaacaaaaa ctaaaactgc aggtccagat caaacagaaa atggactatt 420
gaaggettge ageceacagt ggaagtatgt ggntaggngt etatgeteag aateceaage 480
cggagaaagt cagcettetg gtttagactg cagtaaccaa cattgatege cetaaaggac 540
tggncattca cttggatggt ggatgtccaa ttc
<210> 264
<211> 550
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
\langle 222 \rangle 39, \overline{174}, 352, 526
<223> n = A, T, C or G
<400> 264
tegageggee geeegggeag gteettgeag etetgeagng tettetteac cateaggtge 60
agggaatage teatggatte cateeteagg getegagtag gteaceetgt acetggaaac 120
ttgcccctgt gggctttccc aagcaatttt gatggaatcg acatccacat cagngaatgc 180
cagtccttta gggcgatcaa tgttggttac tgcagtctga. accagagget gactctctcc 240
gcttggattc tgagcataga cactaaccac atactccact gtgggctgca agccttcaat 300
agtcatttct gtttgatctg gacctgcagt tttaagtttt tggtggtcct gncccatttt 360
tgggaagtgg ggggttactc tgtaaccagt aacaggggaa cttgaaggca gccacttgac 420
actaatgctg ttgtcctgaa catcggtcac ttgcatctgg ggatggtttt gacaatttct 480
ggttcggcaa attaatggaa attggcttgc tgcttggcgg ggctgnctcc acgggccagt 540
gacagcatac
<210> 265
<211> 596
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature <222> 347, 352, 353, 534, 555, 587
<223> n = A, T, C or G
<400> 265
tegageggee geeegggeag gteettgeag etetgeagtg tettetteae cateaggtge 60
agggaatage teatggatte catecteagg getegagtag gteaceetgt acetggaaae 120
ttgcccctgt gggctttccc aagcaatttt gatggaatcg acatccacat cagtgaatgc 180
cagteettta gggegateaa tgttggttac tgcagtetga accagagget gaetetetee 240
gcttggattc tgagcataga cactaaccac atactccact gtgggctgca agccttcaat 300
agtcatttct gtttgatctg gacctgcagt tttaagtttt tgttggncct gnnccatttt 360
tggggaaggg gtggttactc ttgtaaccag taacagggga acttgaagca gccacttgac 420
actaatqctg gtggcctgaa catcggtcac ttgcatctgg gatggtttgg tcaatttctg 480
ttcggtaatt aatgggaaat tggcttactg gcttgcgggg gctgtctcca cggncagtga 540
caagcataca caggngatgg gtataatcaa ctccaggttt aaggccnctg atggta
<210> 266
<211> 506
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
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<222> 393, 473
<223> n = A, T, C or G
<400> 266
agcgtggtcg cggccgaggt ctgggatgct cctgctgtca cagtgagata ttacaggatc 60
acttacqqaq aaacaqqaqq aaataqccct qtccaqqaqt tcactqtqcc tqqqaqcaaq 120
tctacagcta ccatcagcgg ccttaaacct ggagttgatt ataccatcac tgtgtatgct 180
qtcactggcc gtggaqacag ccccqcaagc aqtaagccaa tttccattaa ttaccgaaca 240
gaaattgaca aaccatccca gatgcaagtg accgatgttc aggacaacag cattagtgtc 300
aagtggctgc cttcaagttc ccctgttact ggttacagag taaccaccac tcccaaaaat 360
gggaccagga ccaacaaaaa actaaaactg canggtccag atcaaacaga aatgactatt 420
gaaggettge ageceaeagt ggagtatgtg ggttagtgte tatgeteaga atneeaageg 480
gagagagtca gcctctggtt cagact
<210> 267
<211> 548
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 346, 358, 432, 510, 512
<223> n = A, T, C or G
<400> 267
tegageggee geeegggeag gteagegete teaggaegte accaecatgg cetgggetet 60
gctcctcctc accctcctca ctcagggcac agggtcctgg gcccagtctg ccctgactca 120
gcctccctcc gcgtccgggt ctcctggaca gtcagtcacc atctcctgca ctggaaccag 180
cagtgacgtt ggtgcttatg aatttgtctc ctggtaccaa caacacccag gcaaggcccc 240
caaactcatg atttctgagg tcactaagcg gccctcaggg gtccctqatc gcttctctqq 300
ctccaagtct ggcaacacgg cctccctgac cgtctctggg ctccangctg aggatgangc 360
tgattattac tggaagctca tatgcaggca acaacaattg ggtgttcggc ggaagggacc 420
aagctgaccg tnctaaggtc aagcccaagg cttgccccc tcggtcactc tgttcccacc 480
ctcctctgaa gaagctttca agccaacaan gncacactgg gtgtgtctca taagtggact 540
ttctaccc
<210> 268
<211> 584
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 98, \overline{3}80, 421, 454, 495, 506, 512, 561, 565, 579
<223> n = A, T, C or G
<400> 268
agcgtggtcg cggccgaggt ctgtagcttc tgtgggactt ccactgctca ggcgtcaggc 60
tcaggtaget getggeegeg tacttgttgt tgctttgntt ggagggtgtg gtggteteca 120
ctcccgcctt gacgggctg ctatctgcct tccaggccac tgtcacggct cccgggtaga 180
agtcacttat gagacacacc agtgtggcct tgttggcttg aagctcctca gaggagggtg 240
ggaacagagt gaccgagggg gcagccttgg gctgacctag gacggtcagc ttggtccctc 300
cgccgaacac ccaattgttg ttgcctgcat atgagctgca gtaataatca gcctcatcct 360
cagcctggag cccagagacn gtcaagggag gcccgtgttt gccaagactt ggaagccaga 420
naagcgatca gggacccctg agggccgctt tacngacctc aaaaaatcat gaatttgggg 480
ggcctttgcc tgggngttgg ttggtnacca gnaaaacaaa atttcataaa gcaccaacgt 540
cactgctggt ttccagtgca ngaanatggt gaactgaant gtcc
                                                                    584
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PCT/US01/22635

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<210> 269
<211> 368
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 265, 329
<223> n = A, T, C or G
<400> 269
agogtqgtcq cqqccqaqqt ccaqcatcaq qaqcccqcc ttqccqqctc tggtcatcqc 60
ctttcttttt gtggcctgaa acgatgtcat caattcgcag tagcagaact gccgtctcca 120
ctgctgtctt ataagtctgc agettcacag ccaatggctc ccatatgccc agttccttca 180
tgtccaccaa agtacccgtc tcaccattta caccccaggt ctcacagttc tcctgggtgt 240
gettggcccg aagggaggta agtanacgga tggtgctggt cccacagttc tggatcaggg 300
tacgaggaat gacctctagg gcctgggcna caagccctgt atggacctgc ccgggcgggc 360
ccgctcga
                                                                   368
<210> 270
<211> 368
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 54, 163, 219, 229, 316
<223> n = A, T, C or G
<400> 270
tcgagcggcc gcccgggcag gtccatacag ggctgttgcc caggccctag aggncattcc 60
ttgtaccetg atccagaact gtgggaccag caccatccgt ctacttacct cccttcgggc 120
caagcacacc caggagaact gtgagacctg gggtgtaaat ggngagacgg gtactttggt 180
ggacatgaag gaactgggca tatgggagcc attggctgng aagctgcana cttataagac 240
agcagtggag acggcagttc tgctactgcg aattgatgac atcgtttcag gccacaaaaa 300
gaaaggegat gaccanagce ggcaaggegg ggctteetga tgetggaeet eggeegeega 360
ccacgctt
                                                                   368
<210> 271
<211> 424
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 279, 329, 362, 384, 400
<223> n = A, T, C or G
<400> 271
agcgtggtcg cggccgaggt ccactagagg tctgtgtgcc attgcccagg cagagtctct 60
gcgttacaaa ctcctaggag ggcttgctgt gcggagggcc tgctatggtg tgctgcggtt 120
catcatggag agtggggcca aaggctgcga ggttgtggtg tctgggaaac tccgaggaca 180
gagggctaaa tccatgaagt ttgtggatgg cctgatgatc cacagcggag accctgttaa 240
ctactacgtt gacactgctg tgcgccacgt gttgctcana cagggtgtgc tgggcatcaa 300
ggtgaagatc atgctgccct gggacccanc tggcaaaaat ggcccttaaa aaccccttgc 360
cntgaccacg tgaaccattt gtgngaaccc caagatgaan atacttgccc accaccccc 420
attc
                                                                   424
```

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<210> 272
<211> 541
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 422, 442, 510, 513, 515, 525
<223> n = A, T, C or G
<400> 272
tegageggee geeegggeag gtetgeeaag gagaecetgt tatgetgtgg ggaetggetg 60
gggcatggca ggcggctctg gcttcccacc cttctgttct gagatggggg tggtgggcag 120
tateteatet ttgggtteca caatgeteae gtggteagge aggggettet tagggeeaat 180
cttaccagtt gggtcccagg gcagcatgat cttcaccttg atgcccagca caccctgtct 240
gagcaacacg tggcgcacag cagtgtcaac gtagtagtta acagggtctc cgctgtggat 300
catcaggcca tocacaaact toatggattt agoodtotgt cotcggaqtt toccaaaaca 360
ccacaacctc gccagccttt gggccccact tcttcatgaa tgaaaccgca gcacaccatt 420
ancaaggeee tteegeacag gnaageeett eetaaggagt tttgtaaaeg caaaaaaete 480
ttgcctgggg caaatgggca cacagacctn tantnggacc ttggnccgcg aaccaccgct 540
<210> 273
<211> 579
<212> DNA ·
<213> Homo sapiens
<220>
<221> misc feature
<222> 223, 265, 277, 308, 329, 346, 360, 366, 429, 448, 517, 524,
531, 578
<223> n = A, T, C or G
<400> 273
agegtggteg eggeegaggt etggeeetee tggeaagget ggtgaagatg gteaecetgg 60
aaaacccgga cgacctggtg agagaggagt tgttggacca cagggtgctc gtggtttccc 120
tggaactcct ggacttcctg gcttcaaagg cattagggga cacaatggtc tggatggatt 180
gaagggacag cccggtgctc ctggtgtgaa gggtgaacct ggngcccctg gtgaaaatgg 240
aactccaggt caaacaggag cccgngggct tcctggngag agaggacgtg ttggtgcccc 300
tggcccanac ctgcccgggc ggccgctcna aaagccgaaa tccagnacac tggcggccgn 360
tactantgga atccgaactt cggtaccaaa gcttggccgt aatcatggcc atagcttgtt 420
ccctggggng gaaattggta ttccgctncc aattccacac aacataccga acccggaaag 480
cattaaagtg taaaagccct gggggggcct aaatgangtg agcntaactc ncatttaatt 540
ggcgttgcgc ttcactgccc cgcttttcca gtccgggna
                                                                   579
<210> 274
<211> 330
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 171
<223> n = A, T, C or G
<400> 274
tcgagcggcc gcccgggcag gtctgggcca ggggcaccaa cacgtcctct ctcaccagga 60
agcccacggg ctcctgtttg acctggagtt ccattttcac caggggcacc aggttcaccc 120
```

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ttcacaccag gagcaccggg ctgtcccttc aatccatcca gaccattgtg ncccctaatg 180
cctttgaagc caggaagtcc aggagttcca gggaaaccac gagcaccctg tggtccaaca 240
actectetet caccaqqteq teeqqqtttt ceaqqqtqae catetteace aqeettgeea 300
ggagggccag acctcggccg cgaccacgct
                                                                    330
<210> 275
<211> 97
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 2, 3\overline{5}, 72
<223> n = A, T, C or G
<400> 275
anegtggteg eggeegaggt ceteaceaga ggtgneacet acaacateat agtggaggea 60
ctgaaagacc ancagaggca taaggttcgg gaagagg
<210> 276
<211> 610
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 358, 360, 363, 382, 424, 433, 464, 468, 477, 491, 499, 511,
558, 584, 588, 590
<223> n = A, T, C or G
<400> 276
tcgagcggcc gcccgggcag gtccattttc tccctgacgg tcccacttct ctccaatctt 60
gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat gaccacttcc 120
aaageetaag caetggeaca acagtttaaa geetgattea gacattegtt eecacteate 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caageetteg ttgacagagt tgtccacggt aacaacetet teecgaacet tatgeetetg 300
ctggtctttc agtgcctcca ctatgatgtt gtaggtggca cctctggtga ggacctcngn 360
congaacaac gottaagooc gnattotgoa gaataatooc atcacacttg goggoogott 420
cgancatgca tentaaaagg ggeeccaatt teeecettat aagngaanee gtatttneea 480
atttcactgg ncccgccgnt tttacaaacg ncggtgaact ggggaaaaac cctggcggtt 540
acceaacttt aategeentt ggeageacaa teeeceettt tegneeanen tgggegtaaa 600
taaccgaaaa
                                                                    610
<210> 277
<211> 38
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 2, 5, 18, 21, 31
<223> n = A, T, C or G
<400> 277
ancgnggtcg cggccgangt nttttttttt
                                                                    38
<210> 278
<211> 443
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<220>

WO 02/06317 PCT/US01/22635

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<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 156, 212, 233, 245, 327, 331, 336, 361, 364, 381, 391, 397,
419, 437
<223> n = A, T, C or G
<400> 278
agcgtggtcg cggccgaggt ctgaggttac atgcgtggtg gtggacgtga gccacgaaga 60
ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa 120
gccgcgggag gagcagtaca acagcacgta ccgggnggtc agcgtcctca ccgtcctgca 180
ccagaattgg ttgaatggca aggagtacaa gngcaaggtt tccaacaaag ccntcccagc 240
ccccntcgaa aaaaccattt ccaaagccaa agggcagccc cgagaaccac aggtgtacac 300
cctgccccca tcccgggagg aaaagancaa naaccnggtt cagccttaac ttgcttggtc 360
naangctttt tatcccaacg nacttccccc ntggaantgg gaaaaaccaa tgggccaanc 420
cqaaaaacaa ttacaanaac ccc
<210> 279
<211> 348
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 219, 256, 291, 297, 307, 314, 317
<223> n = A, T, C or G
<400> 279
tcgagcggcc gcccgggcag gtgtcggagt ccagcacggg aggcgtggtc ttgtagttgt 60
tetecggetg eccattgete teccaeteca eggegatgte getgggatag aageetttga 120
ccaggcaggt caggctgacc tggttcttgg tcatctcctc ccgggatggg ggcagggtga 180
acacctgggg ttctcggggc ttgccctttg gttttgaana tggttttctc gatgggggct 240
ggaagggett tgttgnaaac cttgcacttg actccttgcc attcacccag ncctggngca 300
ggacggngag gacnetnace acaeggaace gggetggtgg actgetee
<210> 280
<211> 149
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 18, 34, 51, 118, 120, 140
<223> n = A, T, C \text{ or } G
<400> 280
agcqtqqtcq cqqacqanqt cctqtcaqaq tqqnactqqt aqaaqttcca nqaacctqa 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagngn 120
cctggaatgg ggcccatgan atggttgcc
<210> 281
<211> 404
<212> DNA
<213> Homo sapiens
```

```
<221> misc_feature
<222> 383, 386, 388, 393
<223> n = A, T, C or G
<400> 281
tcgagcggcc gcccgggcag gtccaccaca cccaattcct tgctggtatc atggcaqccq 60
ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180
ggaaccgaat atacaattta tgtcattgcc ctgaagaata atcagaagag cgagcccctg 240
attggaagga aaaagacaga cgagcttccc caactggtaa cccttccaca ccccaatctt 300
catggaccag agatettgga tgttcettee acagtteaaa agacceettt eggeaccee 360
cctgggtatg aacctgggaa aanggnantt aanctttcct ggca
<210> 282
<211> 507
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 320, 341, 424, 450, 459, 487, 498
<223> n = A, T, C or G
<400> 282
agcgtggtcg cggccgaggt ctgggatgct cctgctgtca cagtgagata ttacaggatc 60
acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
tctacagcta ccatcagcgg ccttaaacct ggagttgatt ataccatcac tgtgtatgct 180
gtcactggcc gtggagacag ccccgcaagc agcaagccaa tttccattaa ttaccgaaca 240
gaaattqaca aaccatccca qatqcaaqtq accqatqttc aqqacaacaq cattaqtqtc 300
aagtggctgc cttcaaggtn ccctggtact gggttacaga ntaaccacca ctcccaaaaa 360
tggaccagga accacaaaaa cttaaactgc agggtccaga tcaaaacaga aatgactatt 420
gaangettge ageceacagt gggagtatgn gggtagtgne tatgetteag aatecaageg 480
gaaaaangtc aagccttntg ggttcaa
<210> 283
<211> 325
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 216, 292, 303, 304
<223> n = A, T, C or G
<400> 283
tegageggee geeegggeag gteettgeag etetgeagtg tettetteae cateaggtge 60
agggaatage teatggatte cateeteagg getegagtag gteaccetqt acetggaaac 120
ttgcccctgt gggctttccc aagcaatttt gatggaatcg acatccacat cagtgaatgc 180
cagtccttta gggcgatcaa tgttggttac tgcagnctga accagaggct gactctctcc 240
gettggatte tgageataga cactaaceae atacteeaet gtgggetgea ancetteaat 300
aanncatttc tgtttgatct ggacc
<210> 284
<211> 331
<212> DNA
<213> Homo sapiens
<220>
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```
<221> misc feature
\langle 222 \rangle 54, \overline{5}9, 63, 121, 312, 327
<223> n = A, T, C or G
<400> 284
tegageggee geeegggeag gtetggtggg gteetggeae acgeaeatgg gggngttgnt 60
ctnatccagc tgcccagccc ccattggcga gtttgagaag gtgtgcagca atgacaacaa 120
naccttcgac tettectgcc acttetttgc cacaaagtgc accetggagg gcaccaagaa 180
gggccacaag ctccacctgg actacatcgg gccttgcaaa tacatccccc cttgcctgga 240
ctctgagetg accgaattce cccttgegea tgegggaetg geteaagaac egteetggea 300
cccttgtatg anagggatga agacacnacc c
<210> 285
<211> 509
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 316, 319, 327, 329, 339, 344, 357, 384, 398, 427, 443, 450,
478
<223> n = A, T, C or G
<400> 285
agcgtggtcg cggccgaggt ctgtcctaca gtcctcagga ctctactccc tcagcagcgt 60
ggtgaccgtg ccctccagca acttcggcac ccagacctac acctgcaacg tagatcacaa 120
gcccagcaac accaaggtgg acaagagagt tgagcccaaa tcttgtgaca aaactcacac 180
atgcccaccg tgcccagcac etgaacteet ggggggaccg teagtettee tetteccccg 240
cateccectt ccaaacetge eegggeggee getegaaage egaatteeag cacaetggeg 300
geoggtacta qtqqancena acttqqnane caacetqqnq qaantaatqq qcataanetq 360
tttctggggg gaaattggta tccngtttac aattcccnca caacatacga gccggaagca 420
taaaagngta aaagcctggg ggnggcctan tgaagtgaag ctaaactcac attaattngc 480
gttgccgctc actggcccgc ttttccagc
<210> 286
<211> 336
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 188, 251, 267
<223> n = A, T, C or G
<400> 286
tegageggee geeegggeag gtttggaagg gggatgeggg ggaagaggaa gaetgaeggt 60
cccccagga gttcaggtgc tgggcacggt gggcatgtgt gagttttgtc acaagatttg 120
ggctcaactc tettgtccac cttggtgttg ctgggcttgt gatctacgtt gcaggtgtag 180
gtctgggngc cgaagttgct ggagggcacg gtcaccacgc tgctgaggga gtagagtcct 240
gaggactqta ngacagacct cggccqnqac cacgctaagc cgaattctgc aqatatccat 300
cacactggcg gccgctccga gcatgcattt tagagg
<210> 287
<211> 30
<212> DNA
<213> Homo sapiens
<220>
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<221> misc feature
<222> 8, 18
<223> n = A, T, C or G
<400> 287
                                                                   30
agcgtggncg cggacganga caacaaccc
<210> 288
<211> 316
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 22, 130
<223> n = A, T, C or G
<400> 288
togagoggco gocogggcag gnocacatog gcagggtogg agocotggco gccatactog 60
aactggaatc catcggtcat gctcttgccg aaccagacat gcctcttgtc cttggggttc 120
ttgctgatgn accagttctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
ccagteteca tgttgcagaa gaetttgatg gcatecaggt tgcageettg gttggggtca 240
atccagtact ctccactctt ccagtcagag tggcacatct tgaggtcacg gcaggtgcgg 300
gcggggttct tgacct
                                                                   316
<210> 289
<211> 308
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 36, 165, 191, 195, 218, 235
<223> n = A, T, C or G
<400> 289
agegtggteg eggeegaggt ceageetgga gataanggtg aaggtggtge eeeeggaett 60
ccaggtatag ctggacctcg tggtagccct ggtgagagag gtgaaactgg ccctccagga 120
cctgctggtt tccctggtgc tcctggacag aatggtgaac ctggnggtaa aggagaaaga 180
ggggctccgg ntganaaagg tgaaggaggc cctcctgnat tggcaggggc cccangactt 240
agaggtggag ctggcccccc tggccccgaa ggaggaaagg gtgctgctgg tcctcctggg 300
ccacctgg
                                                                   308
<210> 290
<211> 324
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 184
<223> n = A, T, C or G
<400> 290
tegageggee geeegggeag gtetgggeea ggaggaeeaa taggaeeagt aggaeeett 60
gggccatctt tecetgggac accateagea eetggacege etggtteace ettgteacec 120
tttggaccag gacttccaag acctcctctt tctccaggca ttccttgcag accaggagta 180
ccancagcac caggtggccc aggaggacca gcagcaccct ttcctccttc gggaccaggg 240
```

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ggaccaqctc cacctctaag teetggggee cetgecaate caggagggee teetteacet 300
ttctcacccq gagcccctct ttct
<210> 291
<211> 278
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 249, 267
<223> n = A, T, C or G
<400> 291
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atccagaacg agaaggagac catgcaaagc ctgaacgacc gcctggcctc ttacctggac 120
agagtgagga gcctggagac cgacaaccgg aggctggaga gcaaaatccg ggagcacttg 180
gagaagaagg gaccccaggt cagagactgg agccattact tcaagatcat cgaggacctg 240
agggctcana tcttcgcaaa tactgcngac aatgcccg
<210> 292
<211> 299
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 6, 19, 25, 51, 53, 61, 63, 70, 109, 136, 157, 241, 276
<223> n = A, T, C or G
<400> 292
atgcgnggtc gcggccgang accanctctg gctcatactt gactctaaag ncntcaccag 60
nanttacggn cattgccaat ctgcagaacg atgcgggcat tgtccgcant atttgcgaag 120
atctgagece teaggneete gatgatettg aagtaangge teeagtetet gaeetggggt 180
coefficient coaagtgete coggattitg etetecagee teeggttete ggtetecaag 240
ncttctcact ctgtccagga aaagaggcca ggcggncgat cagggctttt gcatggact 299
<210> 293
<211> 101
<212> DNA
<213> Homo sapiens
<400> 293
ttttttttt tttttttt tttttttt ttttttt t
<210> 294
<211> 285
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 64, 103, 110, 237, 282
<223> n = A, T, C or G
<400> 294
tegageggee geeegggeag gtetgeeaac accaagattg geeeeegeeg catecacaca 60
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gttngtgtgc ggggaggtaa caagaaatac cgtgccctga ggntggacgn ggggaatttc 120
tectgggget cagagtgttg tactegtaaa acaaggatea tegatgttgt etacaatgea 180
tctaataacg agctggttcg taccaagacc ctggtgaaga attgcatcgt gctcatngac 240
agcacaccgt accgacagtg ggtaccgaag tcccactatg cncct
<210> 295
<211> 216
<212> DNA
<213> Homo sapiens
<400> 295
togagoggec gecogggeag gtecaceaea eccaatteet tgetggtate atggeageeg 60
ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180
ggaaccgaat atacaattta tgtcattgcc ctgaag.
<210> 296
<211> 414
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 7, 10, 33, 61, 62, 63, 88, 109, 122, 255, 298, 307, 340,
355, 386, 393
<223> n = A, T, C or G
<400> 296
agegtgnten eggeegagga tggggaaget egnetgtett ttteetteea ateagggget 60
nnntcttctg attattcttc agggcaanga cataaattgt atattcggnt cccggttcca 120
gnccagtaat agtagcctct gtgacaccag ggcggggccg agggaccact tctctgggag 180
gagacccagg cttctcatac ttgatgatga agccggtaat cctggcacgt gggcggctgc 240
catgatacca ccaangaatt gggtgtggtg gacctgcccg ggcgggccgc tcgaaaancc 300
gaattentge aagaatatee ateacacttg ggegggeegn tegaaceatg catentaaaa 360
gggccccaat ttccccccta ttaggngaag ccncatttaa caaattccac ttgg
<210> 297
<211> 376
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 312, 326, 335, 361
<223> n = A, T, C or G
<400> 297
tegageggee geeegggeag gtetegeggt egeactggtg atgetggtee tgttggteec 60
coeggecete etggacetee tggteeceet ggteeteea gegetggttt egaetteage 120
ttcctgcccc agccacctca agagaaggct cacgatggtg gccgctacta ccgggctgat 180
gatgccaatg tggttcgtga ccgtgacctc gaggtggaca ccaccctcaa gagccttgag 240
ccagcagaat cqaaaacatt cggaacccaa qaaqqqcaag cccgcaaaqa aaccccqccc 300
gcacctggcc gngaacctcc aagaangtgc ccacntcttg actgggaaaa aaagggaaaa 360
ntacttggaa ttggac
                                                                   376
<210> 298
<211> 357
<212> DNA
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<213> Homo sapiens
<221> misc feature
<222> 345, 346
<223> n = A, T, C or G
<400> 298
agcgtggtcg cggccgaggt ccacatcggc agggtcggag ccctggccgc catactcgaa 60
ctggaatcca teggteatge tetegeegaa ceagacatge etettgteet tggggttett 120
gctgatgtac cagttettet gggccacact gggctgagtg gggtacacgc aggteteace 180
agtctccatg ttgcagaaga ctttgatggc atccaggttg cagccttggt tggggtcaat 240
ccagtactct ccactcttcc agtcagaagt ggcacatctt gaggtcacgg cagggtgcgg 300
geggggttet tgegggetge cettetggge teeeggaatg ttetnngaac ttgetgg
<210> 299
<211> 307
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 281, 285, 306
<223> n = A,T,C or G
<400> 299
agcgtggtcg cggccgaggt ccactagagg tctgtgtgcc attgcccagg cagagtctct 60
gcgttacaaa ctcctaggag ggcttgctgt gcggagggcc tgctatggtg tgctgcggtt 120
catcatggag agtggggcca aaggctgcga ggttgtggtg tctgggaaac tccgaggaca 180
gagggctaaa tccatgaagt ttgtggatgg cctgatgatc cacagcggag accctgttaa 240
ctactacgtt gacacttgct tgtgcgccac gtgttgctca nacangggtg ggctgggcat 300
caaggng
<210> 300
<211> 351
<212> DNA
<213> Homo sapiens
<400> 300
tegageggee geeegggeag gtetgeeaag gagaceetgt tatgetgtgg ggaetggetg 60
gggcatggca ggcggctctg gcttcccacc cttctgttct gagatggggg tggtgggcag 120
tatctcatct ttgggttcca caatgctcac gtggtcaggc aggggcttct tagggccaat 180
cttaccagtt gggtcccagg gcagcatgat cttcaccttg atgcccagca caccctqtct 240
gagcaacacg tggcgcacag caagtgtcaa cgtaagtaag ttaacagggt ctccgctgtg 300
gatcatcagg ccatccacaa acttcatgga tttaaccctc tgtcctcgqa g
<210> 301
<211> 330
<212> DNA
<213> Homo sapiens
<400> 301
tegageggee geeegggeag gtgttteaga ggtteeaagg teeactgtgg aggteeeagg 60
agtgctggtg gtgggcacag aggtccgatg ggtgaaacca ttgacataga gactgttcct 120
gtccagggtg taggggccca gctctttgat gccattggcc agttggctca gctcccagta 180
cagccgctct ctgttgagtc cagggctttt ggggtcaaga tgatggatgc agatggcatc 240
cactccagtg gctgctccat ccttctcgga cctgagagag gtcagtctgc agccagagta 300
cagagggcca acactggtgt tctttgaata
                                                                   330
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<210> 302-
<211> 317
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 129, 295
<223> n = A, T, C or G
<400> 302
agcgtggtcg cggccgaggt ctgtactggg agctaagcaa actgaccaat gacattgaag 60
agetgggccc ctacaccetg gacaggaaca gtetetatgt caatggtttc acceatcaga 120
getetgtgne caccaccage actectggga cetecacagt ggattteaga aceteaggga 180
ctccatcctc cctctccagc cccacaatta tggctgctgg ccctctcctg gtaccattca 240
ccctcaactt caccatcacc aacctgcagt atggggagga catgggtcac cctgnctcca 300
ggaagttcaa caccaca
                                                                   317
<210> 303
<211> 283
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 139, 146, 195
<223> n = A, T, C or G
<400> 303
tegageggee geeeggacag gtetgggegg atageaeegg geatattttg gaatggatga 60
ggtctggcac cctgagcagt ccagcgagga cttggtctta gttgagcaat ttggctagga 120
ggatagtatg cagcacggnt ctgagnctgt gggatagctg ccatgaagta acctgaagga 180
ggtgctggct ggtangggtt gattacaggg ttgggaacag ctcgtacact tgccattctc 240
tgcatatact ggttagtgag gtgagcctgg ccctcttctt ttg
<210> 304
<211> 72
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 59
<223> n = A, T, C or G
<400> 304
agcgtggtcg cggccgaggt gagccacagg tgaccggggc tgaagctggg gctgctggnc 60
ctgctggtcc tg
<210> 305
<211> 245
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 5, 11, 22, 98, 102
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95

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<223> n = A, T, C or G
<400> 305
cagengetee nacggggeet gngggaccaa caacacegtt tteaceetta ggeeetttgg 60
ctcctctttc tcctttagca ccaggttgac cagcagcncc ancaggacca gcaaatccat 120
tggggccagc aggaccgacc tcaccacgtt caccagggct tccccgagga ccagcaggac 180
cagcaggacc agcagcccca gettegeccc ggteacetgt ggeteacete ggeegegace 240
                                                                   245
<210> 306
<211> 246
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 144, 159
<223> n = A, T, C or G
<400> 306
tegageggte geeegggeag gtecaeeggg atageegggg gtetggeagg aatgggagge 60
atccagaacg agaaggagac catgcaaagc ctgaacgacc gcctggcctc ttacctggac 120
agagtgagga gcctggagac cganaaccgg aggctggana gcaaaatccg ggagcacttg 180
gagaagaagg gaccccaggt caagagactg gagccattac ttcaagatca tcgagggacc 240
tggagg
<210> 307
<211> 333
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 5
<223> n = A, T, C or G
<400> 307
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aagacgggca ttgtcaatct gcagaacgat gcgggcattg tccgcagtat ttgcgaagat 120
ctgagccctc aggtcctcga tgatcttgaa gtaatggctc cagtctctga cctggggtcc 180
cttcttctcc aagtgctccc ggattttgct ctccagcctc cggttctcgg tctccaggct 240
ceteactety tecaggtaag aaggeecagg eggtegttea ggetttgeat ggteteette 300
tcgttctgga tgcctcccat tcctgccaga ccc
                                                                   333
<210> 308
<211> 310
<212> DNA
<213> Homo sapiens
<400> 308
tegageggee geeegggeag gteaggaage acattggtet tagageeact geeteetgga 60
ttccacctgt gctgcggaca tctccaggga gtgcagaagg gaagcaggtc aaactgctca 120
gatcagtcag actggctgtt ctcagttctc acctgagcaa ggtcagtctg cagccagagt 180
acagagggcc aacactggtg ttcttgaaca agggcttgag cagaccctgc agaaccctct 240
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ttggtgatgg
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<210> 309

WO 02/06317

96

PCT/US01/22635

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<211> 429
<212> DNA
<213> Homo sapiens
<400> 309
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gctgatgtac cagttcttct gggccacact gggctgagtg gggtacaccg caggtctcac 180
cagtetecat gttgcagaag actttgatgg catecaggtt gcagcettgg ttggggtcaa 240
tocagtactc tocactottc cagtoagaag tgggcacatc ttgaggtcac cggcaggtgc 300
cgggccgggg gttcttgcgg cttgccctct gggctccgga tgttctcgat ctgcttggct 360
caggetettg agggtgggtg tecacetega ggteaeggte aeegaaacet geeeggegg 420
cccgctcga
<210> 310
<211> 430
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 342
<223> n = A,T,C or G
<400> 310
tegageggte geeegggeag gtttegtgae egtgaeeteg aggtggaeae eacceteaag 60
agectgagee ageagatega gaacateegg ageceagagg geageegeaa gaaceeegee 120
cqcacctqcc qtqacctcaa qatqtqccac tctqactqqa aqaqtqqaqa qtactqqatt 180
gaccccaacc aaggctgcaa cctggatgcc atcaaagtct tctgcaacat ggagactggt 240
gagacctgcg tgtaccccac tcagcccagt gtgggcccag aagaaactgg tacatcagca 300
aggaacccca aggacaagag gcattgtctt ggttcggcga gnagcatgac ccgatggatt 360
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gaccaccgct
<210> 311
<211> 2996
<212> DNA
<213> Homo sapiens
<400> 311
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cctacaccct ggacagggac agtctctatg tcaatggttt cacacagegg agctctgtgc 180
ccaccactag catteetggg acceccacag tggacetggg aacatetggg actecagttt 240
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tcaccaacct gcggtatgag gagaacatgc agcaccctgg ctccaggaag ttcaacacca 360
cggagagggt ccttcagggc ctggtccctg ttcaagagca ccagtgttgg ccctctgtac 420
totggotgca gactgacttt gctcaggcct gaaaaggatg ggacagccac tggagtggat 480
gccatctgca cccaccaccc tqaccccaaa aqccctaggc tggacagaga gcaqctqtat 540
tgggagctga gccagctgac ccacaatatc actgagctgg gcccctatgc cctggacaac 600
gacageetet tigteaatgg titeaeteat eggagetetg tgteeaeeae eageaeteet 660
gggaccccca cagtgtatct gggagcatct aagactccag cctcgatatt tggcccttca 720
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cgccctgacc ccacaggccc tgggctggac agagagcagc tgtatttgga gctgagccag 1020
ctgacccaca gcatcactga gctgggccc tacacactgg acagggacag tctctatgtc 1080
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PCT/US01/22635 WO 02/06317

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ggctccctca agttcaacat cacagacaac gtcatgaagc acctgctcag tcctttgttc 1260
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gagetgagte agetgaeeca tggtgteaec caactggget tetatgteet ggaeagggat 1920
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ggagaataca acgtccagca acagtgccca ggctactacc agtcacacct agacctggag 2880
gatetgeaat gaetggaact tgeeggtgee tggggtgeet tteeceeage cagggteeaa 2940
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<210> 312
<211> 914
<212> PRT
<213> Homo sapiens
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Leu Gly Pro Pro Gln Trp Thr Trp Glu His Leu Gly Leu Gln Phe Leu
Asn Leu Val Pro Arg Leu Pro Ala Leu Ser Trp Cys Tyr Ser Leu Ser
                            40
Thr Ser Pro Ser Pro Thr Cys Gly Met Arg Arg Thr Cys Ser Thr Leu
Ala Pro Gly Ser Ser Thr Pro Arg Arg Gly Ser Phe Arg Ala Trp Ser
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70

135

100

Leu Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu

Thr Leu Leu Arg Pro Glu Lys Asp Gly Thr Ala Thr Gly Val Asp Ala

Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Asn Ile Thr Glu Leu

Gly Pro Tyr Ala Leu Asp Asn Asp Ser Leu Phe Val Asn Gly Phe Thr

105 Ile Cys Thr His His Pro Asp Pro Lys Ser Pro Arg Leu Asp Arg Glu 120

90

125

His Arg Ser Ser Val Ser Thr Thr Ser Thr Pro Gly Thr Pro Thr Val Tyr Leu Gly Ala Ser Lys Thr Pro Ala Ser Ile Phe Gly Pro Ser Ala Ala Ser His Leu Leu Ile Leu Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met Trp Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Leu Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro 25<u>0</u> Glu Lys Asp Gly Glu Ala Thr Gly Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Gln Leu Tyr Leu Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Thr Gly Val Val Ser Glu Glu Pro Phe Thr Leu Asn Phe Thr Ile Asn Asn Leu Arg Tyr Met Ala Asp Met Gly Gln Pro Gly Ser Leu Lys Phe Asn Ile Thr Asp Asn Val Met Lys His Leu Leu Ser Pro Leu Phe Gln Arg Ser Ser Leu Gly Ala Arg Tyr Thr Gly Cys Arg Val Ile Ala Leu Arg Ser Val Lys Asn Gly Ala Glu Thr Arg Val Asp Leu Leu Cys Thr Tyr Leu Gln Pro Leu Ser Gly Pro Gly Leu Pro Ile Lys Gln Val Phe His Glu Leu Ser Gln Gln Thr His Gly Ile Thr Arg Leu Gly Pro Tyr Ser Leu Asp Lys Asp Ser Leu Tyr Leu Asn Gly Tyr Asn Glu Pro Gly Pro Asp Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr Phe Leu Pro Pro Leu Ser Glu Ala Thr Thr Ala Met Gly Tyr His Leu Lys Thr Leu Thr Leu Asn Phe Thr Ile Ser Asn Leu Gln Tyr Ser Pro Asp Met Gly Lys Gly Ser Ala Thr Phe Asn Ser Thr Glu Gly Val Leu Gln His Leu Leu Arg Pro Leu Phe Gln Lys Ser Ser Met Gly Pro Phe Tyr Leu Gly Cys Gln Leu Ile Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Thr Thr Cys Thr Tyr His Pro Asp Pro Val Gly Pro Gly Leu Asp Ile Gln Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Val Thr Gln Leu Gly Phe Tyr Val Leu Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr Ala Pro Gln Asn Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn Phe His Ile Val Asn Trp Asn Leu Ser Asn Pro Asp

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615
                                           620
Pro Thr Ser Ser Glu Tyr Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys
                  630
                                      635
Val Thr Thr Leu Tyr Lys Gly Ser Gln Leu His Asp Thr Phe Arg Phe
                                   650
               645
Cys Leu Val Thr Asn Leu Thr Met Asp Ser Val Leu Val Thr Val Lys
           660
                               665
                                                   670
Ala Leu Phe Ser Ser Asn Leu Asp Pro Ser Leu Val Glu Gln Val Phe
                                               685
                           680
Leu Asp Lys Thr Leu Asn Ala Ser Phe His Trp Leu Gly Ser Thr Tyr
                       695
                                           700
Gln, Leu Val Asp Ile His Val Thr Glu Met Glu Ser Ser Val Tyr Gln
                    710
                                       715
Pro Thr Ser Ser Ser Ser Thr Gln His Phe Tyr Leu Asn Phe Thr Ile
                725
                                   730
                                                       735
Thr Asn Leu Pro Tyr Ser Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn
           740
                                745
Tyr Gln Arg Asn Lys Arg Asn Ile Glu'Asp Ala Leu Asn Gln Leu Phe
                           760
                                               765
Arg Asn Ser Ser Ile Lys Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr
                       775
                                           780
Phe Arg Ser Val Pro Asn Arg His His Thr Gly Val Asp Ser Leu Cys
                    790
                                       795
Asn Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu
                805
                                   810
Glu Phe Leu Arg Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr
           820
                               825
Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Phe Pro Asn Arg Asn
                           840
                                               845
Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Leu
                       855
                                           860
Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly
                    870
                                       875
Val Leu Val Thr Thr Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val
                885
                                   890
Gln Gln Gln Cys Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp
            900
                                905
Leu Gln
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<210> 313 <211> 656 <212> DNA <213> Homo sapiens

<400> 313

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<210> 314
<211> 519
<212> DNA
<213> Homo sapiens
<400> 314
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gtcactttgc aggggttggt gaagctgctc ccatccatgt acagctccca gtctactgat 120
gtttaaggat ggtctcggtg gttaggccca ctagaataaa ctgagtccaa tacctctaca 180
cagttatgtt taactgggct ctctgacacc gggaggaagg tggcggggtt taggtgttgc 240
aaacttcaat ggttatgcgg ggatgttcac agagcaagct ttggtatcta gctagtctag 300
cattcattag ctaatggtgt cctttggtat ttattaaaat caccacagca tagggggact 360
ttatgtttag gttttgtcta agagttagct tatctgcttc ttgtgctaac agggctattg 420
ctaccaggga ctttggacat gggggccagc gtttggaaac ctcatctagt ttttttgaga 480
gataggccac tggccttgga cctcggccgc gaccacgct
                                                                   519
<210> 315
<211> 441
<212> DNA
<213> Homo sapiens
<400> 315
cacagagegt ttattgacac caccactect gaaaattggg atttettatt aggtteeect 60
aaaagttccc atgttgatta catgtaaata gtcacatata tacaatgaag gcagtttctt 120
cagaggcaac cagggtttat agtgctaggt aaatgtcatc tcttttgtgc tactgactca 180
ttgtcaaacg tctctgcact gttttcagcc tctccacgtt gcctctgtcc tgcttcttag 240
ttccttcttt gtgacaaacc aaaagaataa gaggatttag aacaggactg cttttcccct 300
atgatttaaa aattocaatg actttogooc ttgggagaaa tttocaagga aatotototo 360
getegetete teegttttee titgtgaget tetgggggag ggttagtggt gaettittga 420
tacgaaaaaa tgcattttgt g
<210> 316
<211> 247
<212> DNA
<213> Homo sapiens
<400> 316
tggcgcggct gctggatttc accttcttgc acctgccggt gagcgcctgg ggtctaaagg 60
ggcgggatac tccattatgg cccctcgccc tgtagggctg gaatagttag aaaaggcaac 120
ccagtctagc ttggtaagaa gagagacatg cccccaacct cggcgccctt tttcctcacg 180
atotgotgto ottacttoag ogactgoagg agottoacot goaagaaaac agoattgago 240
·tgctgac
                                                                   247
<210> 317
<211> 409
<212> DNA
<213> Homo sapiens
<400> 317
tgacagggct cctggagttg ttaagtcacc aagtagctgc aggggatgga cactgcccca 60
cacgatgtgg gatgaacagc agccttggtt tgtagcccag ggtgtccatg gatttgaccc 120
gaatgeteee tggaggeeet gtggegagga caggeaetgg atggteeaga ceetetgget 180
ggaggagtgg tggagccagg actgggcctt cagccatgag ggctagaata acctgacctc 240
ttgcattcta acactgggtc attaatgaca cctttccagt ggatgttgca aaaaccaaca 300
ctgtcaggaa cctggccctg ggagggctca ggtgagctca caaggagagg tcaagccaag 360
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<210> 318
<211> 320
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 6, 1\overline{7}, 24, 271
<223> n = A, T, C or G
<400> 318
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cctcacgagg tcaggggaac ccttgtagaa ctccaccagc agcatcatct cgtgaaggat 120
gtcattggtc aggaagctgt cctggacgta ggccatctcc acatccatgg ggatgccata 180
gtcactgggc ctttgctcgg gaggaggcat cacccagaaa ggcgagatct tggactcggg 240
gcctgggttg ccagaatagt aaggggagca nagcagggcg aggcagggct ggaagccatt 300
gctggagccc tgcagccqca
<210> 319
<211> 212
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 172
<223> n = A, T, C or G
<400> 319
tgaagcaata gcgcccccat tttacaggcg gagcatggaa gccagagagg tgggtggggg 60
agggggtcct tccctggctc aggcagatgg gaagatgagg aagccgctga agacgctgtc 120
ggcctcagag ccctggtaaa tgtgaccctt tttggggtct ttttcaaccc anacctggtc 180
accetgetge agacetegge egegaceaeg et
<210> 320
<211> 769
<212> DNA
<213> Homo sapiens
<400> 320
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tccaactcac cagtgagaga tgagactgcc cagtactcag ccttcatctc ctgggccacc 120
tggagggcgt ctttctccat cagcgcatac tgagcagggg tactcagatc cttcttggaa 180
cctacaagga agagaagcac actggaaggg tcattctcct tcagggcatc ggccagccac 240
tgcctgccat gggaggtgga aagtaaggga tgagtgagtc tgcagggccc ctcccactga 300
cattcatagg cccaattacc ccctctctgg tcctacatgc attcttcttc ttcctgacca 360
cccctctgtt ctgaaccctc tcttcccgga gcctcccatt atattgcagg atgctcactt 420
acttggtatg ttccagagat gccacatcat tcaggttgaa gacaatgatg atggcttgga 480
agagtggcag aaacagcccc aggttgacag ggaagacact actgctcatt tccccaatcc 540
ttccagctcc atatgagaaa gccatgtgca ctctgagacc cacctacccc acttcaccca 600
geocettace ttgageteet ctatagtagg ttgatgeaat geatttgaae eteteetgee 660
cagcggtatc ccaactggaa ggaaggaaga gtgaagcaca ggtatgtatc ttgqqqqqtq 720
tgggtgctgg ggagaaggga tagctggaag gggtgtggaa gcactcaca
<210> 321
<211> 690
<212> DNA
<213> Homo sapiens
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WO 02/06317

102

PCT/US01/22635

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<220>
<221> misc feature
<222> 633, 666
<223> n = A, T, C or G
<400> 321
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cctactcccc cggaggcaac tgggaggtca acgggaagac aatcatcccc tataagaagg 120
gtgcctggtg ttcgctctgc acagccagtg tctcaggctg cttcaaagcc tgggaccatg 180
cagggggget ctgtgaggte cccaggaate cttgtcgcat gagetgccag aaccatggae 240
gteteaacat cagcacetge caetgeeact gteeceetgg ctacaeggge agatactgee 300
aagtgaggtg cagcetgcag tgtgtgcacg gccggttccg ggaggaggag tgctcgtgcg 360
tctgtgacat cggctacggg ggagcccagt gtgccaccaa ggtgcatttt cccttccaca 420
cctgtgacct gaggatcgac ggagactgct tcatggtgtc ttcagaggca gacacctatt 480
acagaagcca ggatgaaatg tcagaggaat ggcggggtgc tggcccagat caagagccag 540
aaagtgcagg acatcctcgc cttctatctg ggccgcctgg agaccaccaa cgaggtgact 600
gacagtgact ttgagaccag gaacttctgg atngggctca cctacaagac cgccaaggac 660
teettneget gggecaeagg ggageaecag
                                                                   690
<210> 322
<211> 104
<212> DNA
<213> Homo sapiens
<400> 322
gtegeaagee ggageaceae catgtageet tteeegaagt aceggaeett etecteetee 60
acqctcacat cacqqacatc atqqaqcaqq accaccacct qqtc
<210> 323
<211> 118
<212> DNA
<213> Homo sapiens
<400> 323
gggccctggg cgcttccaaa tgacccagga ggtggtctgc gacgaatgcc ctaatgtcaa 60
actagtgaat gaagaacgaa cactggaagt agaaatagag cctggggtga gagacgga
<210> 324
<211> 354
<212> DNA
<213> Homo sapiens
<400> 324
tgctctccgg gagcttgaag aagaaactgg ctacaaaggg gacattgccg aatgttctcc 60
ageggtetgt. atggacceag gettgteaaa etgtactata cacategtga eagteaceat 120
taacggagat gatgccgaaa acgcaaggcc gaagccaaag ccaggggatg gagagtttgt 180
ggaagtcatt tctttaccca agaatgacct gctgcagaga cttgatgctc tggtagctga 240
agaacatete acagtggacg ecagggteta tteetacget etagegetga aacatgcaaa 300
tgcaaagcca tttgaagtgc ccttcttgaa attttaagcc caaatatgac actg
<210> 325
<211> 642
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
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PCT/US01/22635

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<222> 1
<223> n = A, T, C or G
<400> 325
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cccactgata ccaagaccaa tgaaagagac acagttaagc agcaatccat ctcatttcca 120
ggcacttcaa taggtcgctg attggtcctt gcaccagcag tggtagtcgt acctatttca 180
gagaggtctg aaattcaggt tcttagtttg ccagggacag gccctacctt atatttttt 240
ccatcttcat catccacttc tgcttacagt ttgctgctta caataactta atgatggatt 300
gagttatctg ggtggtctct agccatctgg gcagtgtggt tctgtctaac caaagggcat 360
tggcctcaaa ccctgcattt ggtttagggg ctaacagagc tcctcagata atcttcacac 420
acatgtaact gctggagatc ttattctatt atgaataaga aacgagaagt ttttccaaag 480
tgttagtcag gatctgaagg ctgtcattca gataacccag cttttccttt tggcttttag 540
cccattcaga ctttgccaga gtcaagccaa ggattgcttt tttgctacag ttttctgcca 600
aatggcctag ttcctgagta cctggaaacc agagagaaag ag
<210> 326
<211> 455
<212> DNA
<213> Homo sapiens
<400> 326
teegtgagga tgagettega gteetteace aggeactgea ggggeacagt caegteaate 60
accttcacct tetegetett cetgetettg teattgacaa actteeegta eeaggeattg 120
acgatgatga ggcccattct ggactcttct gcctcaatta tccttcggac agattcctgc 180
atcagccgga cagcggactc cgcctcttgc ttcttctgca gcacatcggt ggcggcgctt 240
tecetetget tetecaatte ettetette tgageeetga ggtatggttt gatgateaga 300
cggtgcatgg caaagtagac cactagaggc cccacggtgg catagaacat ggcgctgggc 360
agaagctgqt ccgtcaagtg aatagggaag aagtatgtct gactgqccct gttqaqcttg 420
actttgagag aaacgccctg tggaactcca acgct
<210> 327
<211> 321
<212> DNA
<213> Homo sapiens
<400> 327
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ctctctgagt tctcttcaat gatgctgatg atgcagtcca cgataqcgcg cttatactca 120
aagccaccct cttcccgcag catggtgaac aggaagttca taaggacggc gtgtttgcga 180
qqatatttct gacacaqggc actqatqqcc tqqacaacca ccaccttqaa ttcatccqaq 240
atttctgaca tgaaggagga gatctgcttc atgaggcggt cgatgctgct ctcgctgccc 300
gtcttaagga gggtggtgat g
                                                                   321
<210> 328
<211> 476
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 302, 311
<223> n = A, T, C or G
<400> 328
tgcaggaggg gccatggggg ctgtgaatgg gatgcagccc catggtgtcc ctgataaatc 60
cagtgtgcag tctgatgaag tctgggtggg tgtggtctac gggctggcag ctaccatgat 120
ccaagaggta atgcactcct tttcccatct ctccaccatc tgtatcctgg ccmagaaaaa 180
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<400> 333

WO 02/06317 PCT/US01/22635

104

cttcccttca aaccaaccaa aatttccttt caaaggcata acccaaatgc catccttggt 240 coggictaat aaagootooc coattitto cotggiatgo attoccaggo tocctggoot 300 threagggett netgtetgtg ggteatagtt tateteetee eacttgetgg gageteettg 360 aaggcaaaga ctctactgcc tccatctatc cagtggaagt ggctcttcag agggtgccaa 420 gttagtatgt atgactgtca tctctcccaa cagggcctga cttggsaggg cttcca <210> 329 <211> 340 <212> DNA <213> Homo sapiens <400> 329 cgagggagat tgccagcacc ctgatggaga gtgagatgat ggagatcttg tcagtgctag 60 ctaagggtga ccacagccct gtcacaaggg ctgctgcagc ctgcctggac aaagcagtgg 120 aatatgggct tatccaaccc aaccaagatg gagagtgagg gggttgtccc tgggcccaag 180 gctcatgcac acgctaccta ttgtggcacg gagagtaagg acggaagcag ctttggctgg 240 tggtggctgg catgcccaat actcttgccc atcctcgctt gctgccctag gatgtcctct 300 gttctgagtc agcggccacg ttcagtcaca cagccctgct 340 <210> 330 <211> 277 <212> DNA <213> Homo sapiens <400> 330 tgtcaccatc acattggtgc caaataccca gaagacatcg tagatgaaga gtccgcccag 60 caggatgcag ccagtgctga cattgttgag gtgcaggagc tctactccat taagggagaa 120 ggccaggcca aaaaggttgt tggcaatcca gtgcttcctc agcaggtacc agacgccaac 180 gatgctgctc aggcccaggc acaccaggtc cttggtgtca aattcataat tgatgatctc 240 ctccttgttt tcccagaacc ctgtgtgaag agcagac <210> 331 <211> 136 <212> DNA <213> Homo sapiens <400> 331 ttgcttccca cctcctttct ctgtcctctc ctgaggttct gccttacaat ggggacactg 60 atacaaacca cacacacaat gaggatgaaa acagataaca ggtaaaatga cctcacctgc 120 ccgggcggcc gctcga 136 <210> 332 <211> 184 <212> DNA <213> Homo sapiens <400> 332 ttgtgagata aacgcagata ctgcaatgca ttaaaacgct tgaaatactc atcagggatg 60 ttgctgatct tattgttgtc taagtagaga gttagaagag agacagggag accagaaggc 120 agtetggeta tetgattgaa geteaagtea aggtattega gtgatttaag acetttaaaa 180 gcag <210> 333 <211> 384 <212> DNA <213> Homo sapiens

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tcaaaacctc caccaccgtg cgcaccacag agattaactt caaggttggg gaggagtttg 180
aggagcagac tgtggatggg aggccctgta agagcctggt gaaatgggag agtgagaata 240
aaatggtctg tgagcagaag ctcctgaagg gagagggccc caagacctcg tggaccagag 300
aactgaccaa cgatggggaa ctgatcctga ccatgacggc ggatgacgtt gtgtgcacca 360
gggtctacgt ccgagagtga gcgg
<210> 334
<211> 169
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 2, 1\overline{6}5
<223> n = A, T, C or G
<400> 334
cnacaaacag agcagacacc ctggatccgg tcctgctact ggccaggacg gctggaccgt 60
aaaattgaat ttccacttcc tqaccqccqc caqaaqaqat tqattttctc cactatcact 120
agcaagatga acctctctga ggaggttgac ttggaagact atgtngccc
                                                                   169
<210> 335
<211> 185
<212> DNA
<213> Homo sapiens
<400> 335
ccaggtttgc agcccaggct gcacatcagg ggactgcctc gcaatacttc atgctgttgc 60
tgctgactga tggtgctgtg acggatgtgg aagccacacg tgaggctgtg gtqcqtgcct 120
cgaacctgcc catgtcagtg atcattgtgg gtgtgggtgg tgctgacttt gaggccatgg 180
agcag
<210> 336
<211> 358
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 26
<223> n = A, T, C or G
<400> 336
ctgcccetgc cttacggcgg ccaganacac acccaggatg gcattggccc caaacttgga 60
tttgttctca gtcccatcca actccagcat caggttgtcc agtttctctt gctccaccac 120
agagagacct gagctgatga gggctggcgo gatggtggag ttgatgtggt ccactgcctt 180
caggacacct ttgcctaagt aacgctgttt gtctccatcc ctcagctcca gggcctcata 240
gatgeceqta gaggeteeae tqqqeaetge aqeeeggaaa agacetttqg caqtataqaq 300
atccacctcc actgtggggt tcccgcggga gtccaggatc tcccgggccc agatcttc
<210> 337
<211> 271
<212> DNA
<213> Homo sapiens
<220>
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<221> misc_feature
<222> 17
<223> n = A, T, C or G
<400> 337
cacaaagcca ccagccnggg aaatcagaat ttacttgatg caactgactt gtaatagcca 60
gaaatcctgc ccagcatggg attcagaacc tggtctgcaa ccaaatccac cgtcaaagtt 120
catacaggat aaaacaaatt caattgcctt ttccacatta atagcatcaa gcttccccaa 180
caaagccaaa gttgccaccg cacaaaaaga gaatcttgtg tcaatttctc cctactttat 240
aaaagtagat ttttcacatc ccatgaagca g
                                                                    271
<210> 338
<211> 326
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 15, 17, 18
<223> n = A, T, C or G
<400> 338
ctgtgctccc gactngnnca tctcaggtac caccgactgc actgggcggg gccctctggg 60
gggaaaggct ccacggggca gggatacatc tcgaggccag tcatcctctg gaggcagccc 120
aatcaggtca aagattttgc ccaactggtc ggcttcagag tttccacaga agagaggctt 180
tegacgaaac atetetgeaa agatacagee aacaeteeac atgteeacag gtgttgeata 240
tgtggactgc agaagaactt cgggagctcg gtaccagagt gtaacaacca cgggtgtaag 300
tgccatctgg tagctgtaga ttctgg
<210> 339
<211> 260
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 47, \overline{5}4, 60, 69, 90, 91, 96, 113, 117, 119, 195
<223> n = A, T, C or G
<400> 339
ttcacctgag gactcatttc gtgccctttg ttgacttcaa gcaaagncct tcanggtctn 60
caaggacgnc acatttccac ttgcgaatgn nctcanggct catcttgaag aanaagnanc 120
ccaagtgctg gatcccagac tcgggggtaa ccttgtgggt aagagctcat ccagtttatg 180
ctttaggacg tccanctact cgggggagct ggaagcctgc gtggatgcgg ccctgctgga 240
cctcggccgc gaccacgcta
<210> 340
<211> 220
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 15, 18
<223> n = A, T, C or G
<400> 340
ctggaagece ggetnggnet ggeageggaa ggagecagge aggtteaege ageggtgetg 60
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gcagtagegg tageggcact egtetatgte cacacacteg ggccegatet tgeggtaace 120
atcagggcag gtgcactgat aggagccagg caagttatgg cagtcctggc tggggcgaca 180
gtcgtgcagg gcctgggcac actcgtccac atccacacag
<210> 341
<211> 384
<212> DNA
<213> Homo sapiens
<400> 341
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gatggagett cacacgattt cetectgegg cageggegaa ggteetetae tgetacaceg 120
ggcgtcacca gtggcccgtc tgcctcagga actcctccga gtgagggagg agggggctcc 180
tttcccagga tcaaggccac agggaggaag attgcacggg cactgttctg aggaggaagc 240
cccgttggct tacagaagtc atggtgttca taccagatgt gggtagccat cctgaatggt 300
ggcaattata tcacattgag acagaaattc agaaagggag ccagccaccc tggggcagtg 360
aagtgccact ggtttaccag acag
                                                                   384
<210> 342
<211> 245
<212> DNA
<213> Homo sapiens
<400> 342
ctggctaagc tcatcattgt tactggtggg caccatgtcc ttgaagcttc aggcaagcaa 60
tgtaaccaac aagaatgacc ccaagtccat caactctcga gtcttcattg gaaacctcaa 120
cacaqctctq qtqaaqaaat caqatqtqqa qaccatcttc tctaaqtatq qccqtqtqqc 180
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ggcag
<210> 343
<211> 611
<212> DNA
<213> Homo sapiens
ccaaaaaaat caagatttaa tttttttatt tgcactgaaa aactaatcat aactgttaat 60
tctcagccat ctttgaagct tgaaagaaga gtctttggta ttttgtaaac gttagcagac 120
tttcctgcca gtgtcagaaa atcctattta tgaatcctgt cggtattcct tggtatctga 180
aaaaaaatacc aaatagtacc atacatgagt tatttctaag tttgaaaaat aaaaagaaat 240
tgcatcacac taattacaaa atacaagttc tggaaaaaat atttttcttc attttaaaac 300
tttttttaac taataatggc tttgaaagaa gaggcttaat ttgggggtgg taactaaaat 360
caaaagaaat gattgacttg agggtctctg tttggtaaga atacatcatt agcttaaata 420
agcagcagaa ggttagtttt aattatgtag cttctgttaa tattaagtgt tttttgtctg 480
ttttacctca atttgaacag ataagtttgc ctgcatgctg gacatgcctc agaaccatga 540
atagcccgta ctagatcttg ggaacatgga tcttagagtc ctttggaata agttcttata 600
taaatacccc c
<210> 344
<211> 311
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 1, 275, 284, 296, 297, 300
<223> n = A, T, C or G
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<400> 344
nctcgaaaaa gcccaagaca gcagaagcag acacctccag tgaactagca aagaaaagca 60
aagaagtatt cagaaaagag atgtcccagt tcatcgtcca gtgcctgaac ccttaccgga 120
aacctgactg caaagtggga agaattacca caactgaaga ctttaaacat ctggctcgca 180
agctgactca cggtgttatg aataaggagc tgaagtactg taagaatcct gaggacctgg 240
agtgcaatga gaatgtgaaa cacaaaacca aggantacat taanaagtac atgcannaan 300
tttggggctt g
<210> 345
<211> 201
<212> DNA
<213> Homo sapiens
<400> 345
cacacggtca tecegactge caacetggag geecaggeee tgtggaagga geegggeage 60
aatgtcacca tgagtgtgga tgctgagtgt gtgcccatgg tcagggacct tctcaggtac 120
ttctactccc gaaggattga catcaccetg tcgtcagtca agtgcttcca caagctggcc 180
tctgcctatg gggccaggca g
<210> 346
<211> 370
<212> DNA
<213> Homo sapiens
<400> 346
ctgctccagg gcgtggtgtg ccttcgtggc ctctgcctcc tccgaggagc caggctgtgt 60
tctcttcaga atgttctgga gcagcagttt gaggcgggtg atgcgttgga agggcagaat 120
cagaaaggac ttgagggaaa ggcgctggca gacggggtcg ctctccagct tctccaagac 180
ctcccggaaa ttgctgttgc tattcatcag gctctggaag gtgcgttcct gataggtctg 240
gttggtgaca taaggcaggt agacceggeg gaagtetggg gegtggttea ggactaegte 300
acatacttgg aaggaqaaga tattgttctc aaagttctct tccaggtctg aaaggaacgt 360
ggcgctgacg
<210> 347
<211> 416
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 416
<223> n = A, T, C or G
<400> 347
ctgttgtgct gtgtatggac gtgggcttta ccatgagtaa ctccattcct ggtatagaat 60
ccccatttga acaagcaaag aaggtgataa ccatgtttgt acagcgacag gtgtttgctg 120
agaacaagga tgagattgct ttagtcctgt ttggtacaga tggcactgac aatccccttt 180
ctggtgggga tcagtatcag aacatcacag tgcacagaca tctgatgcta ccagattttg 240
atttgctgga ggacattgaa agcaaaatcc aaccaggttc tcaacaggct gacttcctgg 300
atgcactaat cgtgagcatg gatgtgattc aacatgaaac aataggaaag aagtttggag 360
aagaggcata ttgaaatatt cactgacctc aagcagcccg attcagcaaa agtcan
<210> 348
<211> 351
<212> DNA
<213> Homo sapiens
<400> 348
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caqttqqatq ctctcctqqa qqctctqaaa ttqaaacqqq caqqaaataq tctqqcaqcc 120
tctacagcag aagaaacggc aggcaqtqcc cagggacgag caggagacag atgccttcct 180
cttgtctcaa ctgcaaaqag gcgttccttc ctctttcact aatcctcctc agcacagacc 240
ctttacgggt gtcaggctgg gggacagtaa ggtctttccc ttcccacaag gccatatctc 300
aggctgtctc agtgggggga aaccttggac aatacccggg ctttcttggg c
<210> 349
<211> 207
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 1
<223> n = A, T, C or G
<400> 349
ncegggacat etecaceete aacagtggca agaagageet ggagaetgaa eacaaggeet 60
tgaccagtga gattgcactg ctgcagtcca ggctgaagac agagggctct gatctgtgcg 120
acagagtgag cgaaatgcag aagctggatg cacaggtcaa ggagctggtg ctgaagtcgg 180
cggtggaggc tgagcgcctg gtggctg
<210> 350
<211> 323
<212> DNA
<213> Homo sapiens
<400> 350
ccatacaggg ctgttgccca ggccctagag gtcattcctc gtaccctgat ccagaactgt 60
ggggccagca ccatccgtct acttacctcc cttcgggcca agcacaccca ggagaactgt 120
gagacctggg gtgtaaatgg tgagacgggt actttggtgg acatgaagga actgggcata 180
tgggagccat tggctgtgaa gctgcagact tataagacag cagtggagac ggcagttctg 240
ctactgcgaa ttgatgacat cgtttcaggc cacgaaaaga aaggcgatga ccagagccgg 300
caaggegggg cteetgatge tgg
<210> 351
<211> 353
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
\langle 222 \rangle 12, \overline{25}, 39, 42
<223> n = A, T, C or G
<400> 351
egeogeatee entggteeet teeanteeet ttteetttnt engggaaegt gtatgeggtt 60
tgtttttgtt ttgtagggtt tttttccttc tccacctctc cctgtctctt ttgctccatg 120
ttgtccgttt ctgtggggtt aggtttatgt ttttaatcat ctgaggtcac gtctatttcc 180
teeggacteg cetgettggt ggegattete caceggttaa tatggtgegt eeettttte 240
ttttgttgcg aatctgagcc ttcttcctcc agcttctgcc ttttgaactt tgttcttcgg 300
ttctgaaacc atacttttac ctgagtttcc gtgaggctga ggctgtgtgc caa
<210> 352
<211> 467
<212> DNA
<213> Homo sapiens
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PCT/US01/22635

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<400> 352
ctgcccacac tgatcacttg cgagatgtcc ttagggtaca agaacaggaa ttgaagtctg 60
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gtcaagagca agttgacaac tttactctgg atataaatac tgcctatgcc agactcagag 180
gaatcgaaca ggctgttcag agccatgcag ttgctgaaga ggaagccaga aaagcccacc 240
aactctgget ttcagtggag gcattaaagt acagcatgaa gacctcatct gcagaaacac 300
ctactatece getgggtagt geagttgagg ceateaaage caactgttet gataatgaat 360
tcacccaage tttaaccgca getatecete cagagteeet gaccegtggg gtgtacagtg 420
aagagaccct tagagcccgt ttctatgctg ttcaaaaaact ggcccga
<210> 353
<211> 350
<212> DNA
<213> Homo sapiens
<400> 353
etgetgeage caeagtagtt ceteceatgg tgggtggece teetggteet getggeecag 60
gaaatctgtc cccaccagga acagccctg gaaaacggcc ccgtcctcta ccaccttgtg 120
gaaatgctgc acgggaactg cctcctggag gaccagcttt accttcccca gacatttgtc 180
ctgattgtgt agttttcctg gactgcattt caaattgact caggaactgt ttattgcatg 240
gagttacaac aggattctga ccatgaagtt ctcttttagg taacagatcc attaactttt 300
ttgaagatgc ttcagatcca acaccaacaa gggcaaaccc ctttgactgg
<210> 354
<211> 351
<212> DNA
<213> Homo sapiens
<400> 354
atttagatga gatctgaggc atggagacat ggagacagta tacagactcc tagatttaag 60
ttttaggttt tttgcttttc taatcaccaa ttcttatata caatgtatat tttagactcg 120
agcagatgat catcttcatc ttaagtcatt ccttttgact gagtatggca ggattagagg 180
gaatggcagt atagatcaat gtctttttct gtaaagtata ggaaaaacca gagaggaaaa 240
aaagagetga caattggaag gtagtagaaa attgaegata atttettett aacaaataat 300
agttgtatat acaaggaggc tagtcaacca gattttattt gttgagggcg a
<210> 355
<211> 308
<212> DNA
<213> Homo sapiens
<400> 355
ttttggcgca agttttacag attttattaa agtcgaagct attggtcttg gaagatgaaa 60
atgcaaatgt tgatgaggtg gaattgaagc cagatacctt aataaaatta tatcttggtt 120
ataaaaataa gaaattaagg gttaacatca atgtgccaat gaaaaccgaa cagaagcagg 180
aacaagaaac cacacaaa aacatcgagg aagaccgcaa actactgatt caggcggcca 240
tegtgagaat catgaagatg aggaaggtte tgaaacacca geagttaett ggegaggtee 300
tcactcag
<210> 356
<211> 207
<212> DNA
<213> Homo sapiens
<400> 356
ctgtcccaag tgctcccaga aggcaggatt ctgaagacca ctccagcgat atgttcaact 60
atgaagaata ctgcaccgcc aacgcagtca ctgggccttg ccgtgcatcc ttcccacqct 120
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PCT/US01/22635

WO 02/06317

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ggtactttga cgtggagagg aactcctgca ataacttcat ctatggaggc tgccggggca 180
ataagaacag ctaccgctct gaggagg
<210> 357
<211> 188
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 25, \overline{2}9
<223> n = A, T, C or G
<400> 357
tegaceaege cetegtageg catgngetne aggacgatge teagagtgat gaacaeeeeg 60
gtgcggccca cgccagcact gcagtgcacc gtgataggcc catcetgtcc aaactgctcc 120
ttggtcttat gcacctgccc gatgaagtca atgaatccct cgcctgtctt gggcacgccc 180
tgctctgg
<210> 358
<211> 291
<212> DNA
<213> Homo sapiens
<400> 358
ctgggagcat cggcaagcta ctgccttaaa atccgatctc cccgagtgca caatttctgt 60
cccttttaag ggttcacaac actaaagatt tcacatgaaa gggttgtgat tgatttgagc 120
aggcaggcgg tacgtgacag gggctgcatg caccggtggt cagagagaaa cagaacaggg 180
cagggaattt cacaatgttc ttctatacaa tggctggaat ctatgaataa catcagtttc 240
taagttatgg gttgattttt aactactggg tttaggccag gcaggcccag g
<210> 359
<211> 117
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
\langle 222 \rangle 79, \overline{9}8, 100
<223> n = A, T, C or G
<400> 359
gccaccacac tccaqcctgg qcaatacagc aagactgtct caaaaaaaaaa aaaaaaaaa 60
cccaaaaaaa ctcaaaaang taatgaatga tacccaangn gccttttcta gaaaaag
<210> 360
<211> 394
<212> DNA
<213> Homo sapiens
<400> 360
ctgttcctct qqqqtqqtcc aqttctagaq tqqqagaaaq qqaqtcaqqc qcattqqqaa 60
tegtggttee agtetggttg cagaatetge acatttgeea agaaatttte cetgtttgga 120
aagtttgccc cagctttccc gggcacacca ccttttgtcc caagtgtctg ccggtcgacc 180
aatctgcctg ccacacattg accaagccag acccggttca cccagctcga ggatcccagg 240
ttgaagagtg gccccttgag gccctggaaa gaccaatcac tggacttctt cccttgagag 300
tcagaggtca cccgtgattc tgcctgcacc ttatcattga tctgcagtga tttctgcaaa 360
tcaagagaaa ctctgcaggg cactcccctg tttc
                                                                    394
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<210> 361
<211> 394
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 28, 31
<223> n = A,T,C or G
<400> 361
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cagcgaggac ttggtcttag ttgagcaatt tggctaggag gatagtatgc agcacggttc 120
tgagtctgtg ggatagctgc catgaagtaa cctgaaggag gtgctggctg gtaggggttg 180
attacagggt tgggaacagc tcgtacactt gccattctct gcatatactg gttagtgagg 240
tgagcctggc getettettt gegetgaget aaagetacat acaatggett tgtggacete 300
ggccgcgacc acgctaagcc gaattccagc acactggcgg ccgttactag tggatccgag 360
ctcggtacca agcttggcgt aatcatggtc atag
                                                                   394
<210> 362
<211> 268
<212> DNA
<213> Homo sapiens
<400> 362
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agtcactttg caggggttgg tgaagctgct cccatccatg tacagctccc agtctactga 120
tqtttaaqqa tqqtctcqqt qqttaqqccc actaqaataa actqaqtcca atacctctac 180
acagttatgt ttaactgggc tctctgacac cgggaggaag gtggcggggt ttaggtgttg 240
caaacttcaa tggttatgcg gggatgtt
<210> 363
<211> 323
<212> DNA
<213> Homo sapiens
<400> 363
cettgacett tteageaagt gggaaggtgt aateegtete cacagacaag geeaggacte 60
gtttgtaccc gttgatgata gaatggggta ctgatgcaac agttgggtag ccaatctgca 120
gacagacact ggcaacattg cggacaccct ccaggaagcg agaatgcaga gtttcctctg 180
tgatatcaag cacttcaggg ttgtagatgc tgccattgtc gaacacctgc tggatgacca 240
gcccaaagga gaaggggag atgttgagca tgttcagcag cgtggcttcg ctggctccca 300
ctttgtctcc agtcttgatc aga
                                                                   323
<210> 364
<211> 393
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 29
<223> n = A, T, C or G
<400> 364
ccaagetete categteece gtgegeagng getactgggg gaacaagate ggeaageeec 60
acactgtccc ttgcaaggtg acaggccgct gcggctctgt gctggtacgc ctcatcactg 120
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cacccagggg cactggcatc gtctccgcac ctgtgcctaa gaagctgctc atgatggctg 180
gcatcgatga ctgctacacc tcagcccggg gctgcactgc caccctgggc aacttcgcca 240
aggecacett tgatgecatt tetaagacet acagetacet gacecegae etetggaagg 300
agactgtatt caccaagtct ccctatcagg agttcactga ccacctcgtc aagacccaca 360
ccagagtete egtgeagegg acteaggete eag
<210> 365
<211> 371
<212> DNA
<213> Homo sapiens
<400> 365
cctcctcaga gcggtagctg ttcttattgc cccggcagcc tccatagatg aagttattgc 60
aggagttcct ctccacgtca aagtaccagc gtgggaagga tgcacggcaa ggcccagtga 120
ctgcgttggc ggtgcagtat tcttcatagt tgaacatatc gctggagtgg tcttcagaat 180
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gccgcgacca cgctaagccg aattccagca cactggcggc cgttactagt ggatccgagc 300
teggtaceaa gettggegta ateatggtea tagetgttte etgtgtgaaa ttgttateeg 360
ctcacaattc c
<210> 366
<211> 393
<212> DNA
<213> Homo sapiens
<400> 366
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tggcaaccct tttttctgct gtcagctgga gagagatgac taccctgaga atctcatcaa 180
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aaacaaacac cacacgagct gccacaggca tgcccttttc atccttctct gctggatcca 300
gcatgcccaa caggatggca agctcccgat tcctatcatc gatgatggga aaaggtaact 360
tttctgtggg ctcttcacaa ttgtaagcat tga
<210> 367
<211> 327
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 34, 54, 55
<223> n = A, T, C or G
<400> 367
ccagctctgt ctcatacttg actctaaagt cttnagcagc aagacgggca ttgnnaatct 60
gcagaacgat gcgggcattg tccacagtat ttgcgaagat ctgagccctc aggtcctcga 120
tgatcttgaa gtaatggctc cagtctctga cctggggtcc cttcttctcc aagtgctccc 180
ggattttgct ctccagcctc cggttctcgg tctccaggct cctcactctq tccaqqtaaq 240
aggecaggeg gtegtteagg ctttgeatgg teteettete gttetggatg ceteecatte 300
ctgccagacc cccggctatc ccggtgg
<210> 368
<211> 306
<212> DNA
<213> Homo sapiens
<220>
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114

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<221> misc feature
<222> 24
<223> n = A, T, C or G
<400> 368
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cctgtgaacc aagtgtttgg gcaggatgag atgatcgacg tcatcggggt gaccaagggc 240
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cgagga
<210> 369
<211> 394
<212> DNA
<213> Homo sapiens
<400> 369
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cacaggcaga ggctggatcc tcaaagttca cattccggac ctcacactgg aacacatctt 300
tgttccttgt aacaaaaggc acttcaattt cagaggcatt cttaacaaac acggcgttag 360
ccactgtcac aatgtcttta ttcttcttgg agac
<210> 370
<211> 653
<212> DNA
<213> Homo sapiens
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ctggtgtcac agaggctact attactggcc tggaaccggg aaccgaatat acaatttatg 180
tcattgccct gaagaataat cagaagagcg agcccctgat tggaaggaaa aaqacagacq 240
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tteetteeac agtteaaaag acceettteg teacceacee tgggtatgae actggaaatg 360
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aggaacatgg ttttaggcgg accacaccgc ccacaacggc cacccccata aggcataggc 480
caagaccata cccgccgaat gtaggacaag aagctctctc tcagacaacc atctcatggg 540
ccccattcca ggacacttct gagtacatca tttcatgtca tcctgttggc actgatgaag 600
aaccettaca gttcagggtt cetggaactt ctaccagtge cactetgaca gga
<210> 371
<211> 268
<212> DNA
<213> Homo sapiens
<400> 371
ctgcccagcc cccattggcg agtttgagaa ggtgtgcagc aatgacaaca agaccttcga 60
ctcttcctgc cacttctttg ccacaaagtg caccctggag ggcaccaaga agggccacaa 120
getecacetg gactacateg ggeettgeaa atacateece cettgeetgg actetgaget 180
gaccgaattc cccctgcgca tgcgggactg gctcaagaac gtcctggtca ccctgtatqa 240
gagggatgag gacaacaacc ttctgact
                                                                   268
<210> 372
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<211> 392

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<212> DNA
<213> Homo sapiens
<400> 372
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ggagataagg gtgaaggtgg tgccccgga cttccaggta tagctggacc tcgtggtagc 360
cctggtgaga gaggtgaaac ctcggccgcg ac
<210> 373
<211> 388
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 30
<223> n = A, T, C or G
<400> 373
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<210> 374
<211> 393
<212> DNA
<213> Homo sapiens
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aagggttgga tgggctgtct gagcgctgtg cccagtacaa qaaggacgga gctgacttcq 240
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aaaatgccaa tgttctggcc cgttatgcca gtatctgcca gcagaatggc attgtgccca 360
tcgtggagcc tgagatcctc cctgatgggg acc
                                                                   393
<210> 375
<211> 394
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222>30, \overline{3}3
<223> n = A, T, C or G
<400> 375
ccacaaatgg cgtggtccat gtcatcacen ttnttctgca gcctccagcc aacagacctc 60
aggaaagagg ggatgaactt gcagactctg cgcttgagat cttcaaacaa gcatcagcgt 120
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PCT/US01/22635

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tttccagggc ttcccagagg tctgtgcgac tagcccctgt ctatcaaaag ttattagaga 180
ggatgaagca ttagettgaa gcactacagg aggaatgcac cacggcagct ctccgccaat 240
ttctctcaga tttccacaga gactgtttga atgttttcaa aaccaagtat cacactttaa 300
tgtacatggg ccgcaccata atgagatgtg agccttgtgc atgtggggga ggagggagag 360
agatgtactt tttaaatcat gttcccccta aaca
<210> 376
<211> 392
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 30
<223> n = A, T, C \text{ or } G
<400> 376
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ctcttcctgc cacttctttg ccacaaagtg caccctggag ggcaccaaga agggccacaa 120
getecacetg gactacateg ggeettgeaa atacateeee eettgeetgg actetgaget 180
gaccqaattc cccctgcgca tgcgggactg gctcaagaac gtcctggtca ccctgtatga 240
gagggatgag gacaacaacc ttctgactga gaagcagaag ctgcgggtga agaagatcca 300
tgagaatgag aagcgcctgg aggcaggaga ccaccccgtg gagctgctgg cccgggactt 360
cgagaagaac tataacatgt acatcttccc tg
<210> 377
<211> 292
<212> DNA
<213> Homo sapiens
<400> 377
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ttgaagtgtt gcatgggcat gtgtgggaaa tcctgcgttt cccctgtgaa agcttgattc 120
ctgccatatg gaggaggctc tggagtcctg ctctgtgtgg tccaggtcct ttccaccctg 180
agacttggct ccaccactga tatcctcctt tggggaaagg cttggcacac agcaggcttt 240
caagaagtgc cagttgatca atgaataaat aaacgagcct atttctcttt gc
<210> 378
<211> 395
<212> DNA
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WO 02/06317

118

PCT/US01/22635

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121

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122

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WO 02/06317 PCT/US01/22635

Phe Ile Asn Gly Tyr Ala Pro Gln Asn Leu Ser Ile Arg Gly Glu Tyr 520 525 Gln Ile Asn Phe His Ile Val Asn Trp Asn Leu Ser Asn Pro Asp Pro 535 Thr Ser Ser Glu Tyr Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys Val 550 555 560 Thr Thr Leu Tyr Lys Gly Ser Gln Leu His Asp Thr Phe Arg Phe Cys 565 570 Leu Val Thr Asn Leu Thr Met Asp Ser Val Leu Val Thr Val Lys Ala 580 585 Leu Phe Ser Ser Asn Leu Asp Pro Ser Leu Val Glu Gln Val Phe Leu 595 600 Asp Lys Thr Leu Asn Ala Ser Phe His Trp Leu Gly Ser Thr Tyr Gln 610 615 620 Leu Val Asp Ile His Val Thr Glu Met Glu Ser Ser Val Tyr Gln Pro 630 635 Thr Ser Ser Ser Ser Thr Gln His Phe Tyr Leu Asn Phe Thr Ile Thr 645 650 Asn Leu Pro Tyr Ser Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe Arg 675 680 685 Asn Ser Ser Ile Lys Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe 690 695 700 Arg Ser Val Pro Asn Arg His His Thr Gly Val Asp Ser Leu Cys Asn 715 705 710 Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu Glu 725 730 Phe Leu Arg Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr Leu 745 Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Phe Pro Asn Arg Asn Glu 755 . 760 Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Leu Ile 775 780 Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly Val 785 790 795 800 Leu Val Thr Thr Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln 805 810 815 Gln Gln Cys Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln

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<400> 390

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Leu Ser Gln Leu Thr His Gly Val Thr Gln Leu Gly Phe Tyr Val Leu
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Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr Ala Pro Gln Asn Leu Ser
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Ile Arg Gly Glu Tyr Gln Ile Asn Phe His Ile Val Asn Trp Asn Leu
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Ser Asn Pro Asp Pro Thr Ser Ser Glu Tyr Ile Thr Leu Leu Arg Asp
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Ile Gln Asp Lys Val Thr Thr Leu Tyr Lys Gly Ser Gln Leu His Asp
            165 170 175
Thr Phe Arg Phe Cys Leu Val Thr Asn Leu Thr Met Asp Ser Val Leu
          180 185 190
Val Thr Val Lys Ala Leu Phe Ser Ser Asn Leu Asp Pro Ser Leu Val
      195
                       200 205
Glu Gln Val Phe Leu Asp Lys Thr Leu Asn Ala Ser Phe His Trp Leu
                   215
                                      220
Gly Ser Thr Tyr Gln Leu Val Asp Ile His Val Thr Glu Met Glu Ser
225
                 230
                                  235
Ser Val Tyr Gln Pro Thr Ser Ser Ser Ser Thr Gln His Phe Tyr Leu
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Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser Gln Asp Lys Ala Gln Pro
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          260
Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg Asn Ile Glu Asp Ala Leu
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Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys Ser Tyr Phe Ser Asp Cys
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Gln Val Ser Thr Phe Arg Ser Val Pro Asn Arg His His Thr Gly Val
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Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val
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                              330
Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr Arg Asn Gly Thr Gln Leu
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Gln Asn Phe Thr Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Phe
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                        360
Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe Trp
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                                     380
Ala Val Ile Leu Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys
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Leu Ile Cys Gly Val Leu Val Thr Thr Arg Arg Arg Lys Lys Glu Gly
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<212> DNA

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126

tagcatcatc attattctgg ctggagcaat tgcactcatc attggctttg gtatttcagg 180 gagacactcc atcacagtca ctactgtcgc ctcagctggg aacattgggg aggatggaat 240 cctgagctgc acttttgaac ctgacatcaa actttctgat atcgtgatac aatggctgaa 300 ggaaggtgtt ttaggettgg tecatgagtt caaagaagge aaagatgage tgteggagea 360 ggatgaaatg ttcagaggcc qqacaqcagt qtttqctqat caaqtqatag ttqqcaatqc 420 ctctttgcgg ctgaaaaacg tgcaactcac agatgctggc acctacaaat gttatatcat 480 cacttctaaa ggcaagggga atgctaacct tgagtataaa actggagcct tcaqcatgcc 540 ggaagtgaat gtggactata atgccagctc agagaccttg cggtgtgagg ctccccgatg 600 gttcccccag cccacagtgg tctgggcatc ccaagttgac cagggagcca acttctcgga 660 agtctccaat accagetttg agetgaacte tgagaatgtg accatgaagg ttgtgtctgt 720 gctctacaat gttacgatca acaacacata ctcctgtatg attgaaaatg acattgccaa 780 agcaacaggg gatatcaaag tgacagaatc ggagatcaaa aggcggagtc acctacagct 840 gctaaactca aaggettete tgtgtgtete ttetttettt gccateaget gggcaettet 900 gcctctcagc ccttacctga tgctaaaata atgtgccttg gccacaaaaa agcatgcaaa 960 gtcattgtta caacagggat ctacagaact atttcaccac cagatatgac ctagttttat 1020 atttctggga ggaaatgaat tcatatctag aagtctggag tgagcaaaca agagcaagaa 1080 acaaaaagaa gccaaaagca gaaggctcca atatgaacaa gataaatcta tcttcaaaga 1140 catattagaa gttgggaaaa taattcatgt gaactagaca agtgtgttaa gagtgataag 1200 taaaatgcac gtggagacaa gtgcatcccc agatetcagg gacetecece tgeetgteac 1260 ctggggagtg agaggacagg atagtgcatg ttctttgtct ctgaattttt agttatatgt 1320 gctgtaatgt tgctctgagg aagcccctgg aaagtctatc ccaacatatc cacatcttat 1380 attocacaaa ttaagotgta gtatgtacco taagacgotg ctaattgact gccacttogc 1440 aactcagggg cggctgcatt ttagtaatgg gtcaaatgat tcacttttta tgatgcttcc 1500 aaaggtgcct tggcttctct tcccaactga caaatgccaa agttgagaaa aatgatcata 1560 attttagcat aaacagagca gtcggcgaca ccgattttat aaataaactg agcaccttct 1620 ttttaaacaa acaaatgcgg gtttatttct cagatgatgt tcatccgtga atggtccagg 1680 gaaggacctt tcaccttgac tatatggcat tatgtcatca caagctctga ggcttctcct 1740 ttccatcctg cgtggacagc taagacctca gttttcaata gcatctagag cagtgggact 1800 cagctggggt gatttcgccc cccatctccg ggggaatgtc tgaagacaat tttggttacc 1860 tcaatgaggg agtggaggag gatacagtgc tactaccaac tagtggataa aggccaggga 1920 tgctgctcaa cctcctacca tgtacaggac gtctccccat tacaactacc caatccgaag 1980 tgtcaactgt gtcaggacta agaaaccctg gttttgagta gaaaagggcc tggaaagagg 2040 ggagccaaca aatctgtctg cttcctcaca ttagtcattg gcaaataagc attctgtctc 2100 tttggctgct gcctcagcac agagagccag aactctatcg ggcaccagga taacatctct 2160 cagtgaacag agttgacaag gcctatggga aatgcctgat gggattatct tcagcttgtt 2220 gagettetaa gtttetttee etteatteta eeetgeaage caagttetgt aagagaaatg 2280 cctgagttct agetcaggtt ttettactct gaatttagat etccagacce tteetggeca 2340 caattcaaat taaggcaaca aacatatacc ttccatgaag cacacacaga cttttgaaag 2400 caaggacaat gactgcttga attgaggcct tgaggaatga agctttgaag gaaaagaata 2460 ctttgtttcc agccccttc ccacactctt catgtgttaa ccactgcctt cctggacctt 2520 ggagccacgg tgactgtatt acatgttgtt atagaaaact gattttagag ttctgatcgt 2580 tcaagagaat gattaaatat acatttccta caccaaaaaa aaaaaaa 2627

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Gln Ile Leu Phe Trp Ser Ile Ile Ser Ile Ile Ile Ile Leu Ala Gly 35 40 45

Ala Ile Ala Leu Ile Ile Gly Phe Gly Ile Ser Gly Arg His Ser Ile 50 55 60 .

Thr Val Thr Thr Val Ala Ser Ala Gly Asn Ile Gly Glu Asp Gly Ile

127

70 75 Leu Ser Cys Thr Phe Glu Pro Asp Ile Lys Leu Ser Asp Ile Val Ile 90 Gln Trp Leu Lys Glu Gly Val Leu Gly Leu Val His Glu Phe Lys Glu 105 Gly Lys Asp Glu Leu Ser Glu Gln Asp Glu Met Phe Arg Gly Arg Thr 120 Ala Val Phe Ala Asp Gln Val Ile Val Gly Asn Ala Ser Leu Arg Leu 135 Lys Asn Val Gln Leu Thr Asp Ala Gly Thr Tyr Lys Cys Tyr Ile Ile 145 150 155 Thr Ser Lys Gly Lys Gly Asn Ala Asn Leu Glu Tyr Lys Thr Gly Ala 170 165 Phe Ser Met Pro Glu Val Asn Val Asp Tyr Asn Ala Ser Ser Glu Thr 185 190 Leu Arg Cys Glu Ala Pro Arg Trp Phe Pro Gln Pro Thr Val Val Trp 200 Ala Ser Gln Val Asp Gln Gly Ala Asn Phe Ser Glu Val Ser Asn Thr 215 Ser Phe Glu Leu Asn Ser Glu Asn Val Thr Met Lys Val Val Ser Val 230 235 Leu Tyr Asn Val Thr Ile Asn Asn Thr Tyr Ser Cys Met Ile Glu Asn 250 245 Asp Ile Ala Lys Ala Thr Gly Asp Ile Lys Val Thr Glu Ser Glu Ile 265 260 Lys Arg Arg Ser His Leu Gln Leu Leu Asn Ser Lys Ala Ser Leu Cys 280 Val Ser Ser Phe Phe Ala Ile Ser Trp Ala Leu Leu Pro Leu Ser Pro Tyr Leu Met Leu Lys 305

<210> 393

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<212> PRT

<213> Homo sapiens

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155
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Ala Ser Ser Glu Thr Leu Arg Cys Glu Ala Pro Arg Trp Phe Pro Gln
          165 170
Pro Thr Val Val Trp Ala Ser Gln Val Asp Gln Gly Ala Asn Phe Ser
                         185
                                  190
Glu Val Ser Asn Thr Ser Phe Glu Leu Asn Ser Glu Asn Val Thr Met
   195 200
Lys Val Val Ser Val Leu Tyr Asn Val Thr Ile Asn Asn Thr Tyr Ser
 210 215 220
Cys Met Ile Glu Asn Asp Ile Ala Lys Ala Thr Gly Asp Ile Lys Val
225 230 235
Thr Glu Ser Glu Ile Lys Arg Arg Ser His Leu Gln Leu Leu Asn Ser
      245 250 255
Lys Ala Ser Leu Cys Val Ser Ser Phe Phe Ala Ile Ser Trp Ala Leu
  260 265 270
Leu Pro Leu Ser Pro Tyr Leu Met Leu Lys
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Ile Ile Leu Ala
<210> 395
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Ile Ile Ile Leu Ala Gly Ala Ile Ala Leu Ile Ile Gly Phe Gly Ile
 1 5
Ser Gly Arg His
<210> 396
<211> 20
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<213> Homo sapiens
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Asn Ile Gly Glu
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<210> 397
<211> 20
<212> PRT
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Asp Ile Lys Leu Ser Asp Ile Val Ile Gln Trp Leu Lys Glu Gly Val
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Leu Gly Leu Val
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Glu Gln Asp Glu
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Gln Val Ile Val
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Leu Thr Asp Ala
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<210> 402 .

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Val Gln Leu Thr Asp Ala Gly Thr Tyr Lys Cys Tyr Ile Ile Thr Ser
1 5
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Lys Gly Lys Gly Asn
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<212> PRT
<213> Homo sapiens
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Lys Gly Lys Gly Asn Ala Asn Leu Glu Tyr Lys Thr Gly Ala Phe Ser
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Met Pro Glu Val
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Arg Cys Glu Ala
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Leu Arg Cys Glu Ala Pro Arg Trp Phe Pro Gln Pro Thr Val Val Trp
1 5
Ala Ser Gln Val
<210> 406
<211> 20
<212> PRT
<213> Homo sapiens
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Trp Ala Ser Gln Val Asp Gln Gly Ala Asn Phe Ser Glu Val Ser Asn
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Thr Ser Phe Glu
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Asn Thr Ser Phe Glu Leu Asn Ser Glu Asn Val Thr Met Lys Val Val
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Ser Val Leu Tyr
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Val Ser Val Leu Tyr Asn Val Thr Ile Asn Asn Thr Tyr Ser Cys Met
1 5
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Ile Glu Asn Asp
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<213> Homo sapiens
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Glu Ser Glu Ile
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1 5
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Lys Ala Ser Leu
          20
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<213> Homo sapiens
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Ser Lys Ala Ser Leu Cys Val Ser Ser Phe Phe Ala Ile Ser Trp Ala
1 5
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Leu Leu Pro Leu
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132

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<211> 20
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<213> Homo sapiens
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Leu Met Leu Lys
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<212> PRT
<213> Homo sapiens
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Lys Leu Ser
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<210> 414
<211> 35
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<213> Homo sapiens
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Glu Gln Asp Glu Met Phe Arg Gly Arg Thr Ala Val Phe Ala Asp Gln
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Val Ile Val
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Cys Glu Ala Pro Arg Trp Phe Pro Gln Pro Thr Val Val Trp Ala Ser
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Glu
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133

PCT/US01/22635

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Lys Leu Ser Asp Ile Val Ile Gln Trp Leu
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Ser Leu Gly Gln Ile Leu Phe Trp Ser Ile
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Leu Leu Asn Ser Lys Ala Ser Leu Cys Val
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Ser Leu Cys Val Ser Ser Phe Phe Ala Ile
<210> 420
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Val Leu Tyr Asn Val Thr Ile Asn Asn Thr
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<213> Homo sapiens ·

134

PCT/US01/22635

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Cys Met Ile Glu Asn Asp Ile Ala Lys Ala
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Lys Thr Gly Ala Phe Ser Met Pro Glu Val
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Trp Ala Leu Leu Pro Leu Ser Pro Tyr Leu
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<212> PRT

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PCT/US01/22635

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Gln Leu Leu Asn Ser Lys Ala Ser Leu Cys
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Ile Leu Ser Cys Thr Phe Glu Pro Asp Ile
    5
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Trp Leu Lys Glu Gly Val Leu Gly Leu Val
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136

PCT/US01/22635

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Gly Ile Ser Gly Arg His Ser Ile Thr Val
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Phe Glu Pro Asp Ile Lys Leu Ser Asp Ile
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Ala Leu Leu Pro Leu Ser Pro Tyr Leu
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Ser Leu Cys Val Ser Ser Phe Phe Ala
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Ile Leu Phe Trp Ser Ile Ile Ser Ile
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<210> 439

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Asn Val Thr Met Lys Val Val Ser Val
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138

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Leu Leu Pro Leu Ser Pro Tyr Leu Met
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PCT/US01/22635 WO 02/06317 139

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Ile Ala Leu Ile Ile Gly Phe Gly Ile
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Cys Thr Phe Glu Pro Asp Ile Lys Leu
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Ile Val Gly Asn Ala Ser Leu Arg Leu
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<212> DNA

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<213> Homo sapiens

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  gaccccaaaa gccctggact ggacagagag cggctgtact ggaagctgag ccagctgacc 180
  cacggcatca ctgagctggg cccctacacc ctggacaggc acagtctcta tgtcaatggt 240
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141

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142

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Phe Thr His Gln Ser Ser Met Thr Thr Thr Arg Thr Pro Asp Thr Ser
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Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Val Phe
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Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu
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Glu Arg Val Leu Gln Gly Leu Leu Arg Ser Leu Phe Lys Ser Thr Ser

143

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144

PCT/US01/22635

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Arg	His	Ser	Leu	Tyr 85	Val	Asn	Gly	Phe	Thr 90	His	Gln	Ser	Ser	Met 95	Thr
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	130			Asn		135					140				
Met 145	His	His	Pro	Gly	Ser 150	Arg	Lys	Phe	Asn	Thr 155	Thr	Glu	Arg	Val	Leu 160
	_			Arg 165				•	170				-	175	
			180	Arg				185					190		
		195		Asp			200		_	-		205		_	
	210			Arg		215					220				
225				Glu	230					235					240
				Phe 245					250					255	
			260	Thr				265			=		270		
		275		Ser			280					285			
	290			Thr		295					300			,	
305				Phe	310					315			_		320
				Lys 325					330			_		335	_
			340	Leu	_			345	_	_			350	_	
		355		Thr			360					365			
	370			Tyr		375					380				
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				Ser 405					410				_	415	
			420	Gly				425					430	_	
		435		His			440					445			
	450			Tyr		455					460		_	_	
465				Arg Gly	470					475					480
41011	****	JUL	AGI	OTA	0	שטע	* A *	26T	GTA	26T	nr 9	π¢α	TILL	ъ÷п	₽eu

146

485 490 Arg Pro Glu Lys Asp Gly Glu Ala Thr Gly Val Asp Ala Ile Cys Thr 505 His Arg Pro Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Gln Leu Tyr 520 Leu Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly Pro Tyr 535 540 Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn Gly Phe Thr His Arg Ser 550 555 Ser Val Pro Thr Thr Ser Thr Gly Val Val Ser Glu Glu Pro Phe Thr 565 570 Leu Asn Phe Thr Ile Asn Asn Leu Arg Tyr Met Ala Asp Met Gly Gln 585 Pro Gly Ser Leu Lys Phe Asn Ile Thr Asp Asn Val Met Lys His Leu 600 Leu Ser Pro Leu Phe Gln Arg Ser Ser Leu Gly Ala Arg Tyr Thr Gly 615 Cys Arg Val Ile Ala Leu Arg Ser Val Lys Asn Gly Ala Glu Thr Arg 630 Val Asp Leu Leu Cys Thr Tyr Leu Gln Pro Leu Ser Gly Pro Gly Leu 645 650 Pro Ile Lys Gln Val Phe His Glu Leu Ser Gln Gln Thr His Gly Ile 665 Thr Arg Leu Gly Pro Tyr Ser Leu Asp Lys Asp Ser Leu Tyr Leu Asn 680 685 Gly Tyr Asn Glu Pro Gly Leu Asp Glu Pro Pro Thr Thr Pro Lys Pro 695 700 Ala Thr Thr Phe Leu Pro Pro Leu Ser Glu Ala Thr Thr Ala Met Gly 710 715 Tyr His Leu Lys Thr Leu Thr Leu Asn Phe Thr Ile Ser Asn Leu Gln 730 725 Tyr Ser Pro Asp Met Gly Lys Gly Ser Ala Thr Phe Asn Ser Thr Glu 740 745 Gly Val Leu Gln His Leu Leu Arg Pro Leu Phe Gln Lys Ser Ser Met 760 Gly Pro Phe Tyr Leu Gly Cys Gln Leu Ile Ser Leu Arg Pro Glu Lys 780 Asp Gly Ala Ala Thr Gly Val Asp Thr Thr Cys Thr Tyr His Pro Asp 790 795 Pro Val Gly Pro Gly Leu Asp Ile Gln Gln Leu Tyr Trp Glu Leu Ser 805 · 810 Gln Leu Thr His Gly Val Thr Gln Leu Gly Phe Tyr Val Leu Asp Arg 820 825 Asp Ser Leu Phe Ile Asn Gly Tyr Ala Pro Gln Asn Leu Ser Ile Arg 840 Gly Glu Tyr Gln Ile Asn Phe His Ile Val Asn Trp Asn Leu Ser Asn 855 860 · Pro Asp Pro Thr Ser Ser Glu Tyr Ile Thr Leu Leu Arg Asp Ile Gln 870 875 Asp Lys Val Thr Thr Leu Tyr Lys Gly Ser Gln Leu His Asp Thr Phe 885 890 895 Arg Phe Cys Leu Val Thr Asn Leu Thr Met Asp Ser Val Leu Val Thr 905 Val Lys Ala Leu Phe Ser Ser Asn Leu Asp Pro Ser Leu Val Glu Gln 920 Val Phe Leu Asp Lys Thr Leu Asn Ala Ser Phe His Trp Leu Gly Ser 935 940 Thr Tyr Gln Leu Val Asp Ile His Val Thr Glu Met Glu Ser Ser Val

147

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<212> PRT

<213> Homo sapiens

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148

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Phe Thr His Gln Ser Ser Met Thr Thr Thr Arg Thr Pro Asp Thr Ser
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Thr Met His Leu Ala Thr Ser Arg Thr Pro Ala Ser Leu Ser Gly Pro
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Thr Thr Ala Ser Pro Leu Leu Val Leu Phe Thr Ile Asn Phe Thr Ile
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Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Val Phe
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Thr Tyr Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Gln Leu
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785		770					775	_	_	_		780		_		-
Leu Gly Phe Tyr Val Leu Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr 820 Ala Pro Gln Asn Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn Phe His 830 Ala Pro Gln Asn Trp Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser Glu Tyr 850 Ile Val Asn Trp Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser Glu Tyr 865 Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys Val Thr Thr Leu Tyr Lys 865 Gly Ser Gln Leu His Asp Thr Phe Arg Phe Cys Leu Val Thr Asn Leu 895 Thr Met Asp Ser Val Leu Val Thr Val Lys Ala Leu Phe Ser Ser Asn 910 Leu Asp Pro Ser Leu Val Glu Gln Val Phe Leu Asp Lys Thr Leu Asn 915 Ala Ser Phe His Trp Leu Gly Ser Thr Tyr Gln Leu Val Asp Ile His 930 Val Thr Glu Met Glu Ser Ser Val Tyr Gln Leu Val Asp Ile His 930 Thr Gln His Phe Tyr Pro Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser 965 Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg 980 Asn Ile Glu Asp Ala Leu Asn Gln Leu Asn Gln Leu Asn 985 Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn 1010 Arg His His Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala		Thr	Суѕ	Thr	Tyr		Pro	Asp	Pro	Val	_	Pro	Gly	Leu	Asp	
Record R	Gln	Gln	Leu	Tyr	_	Glu	Leu	Ser	Gln		Thr	His	Gly	Val		Gln
Sas	Leu	Gly	Phe		Val	Leu	Asp	Arg	_	Ser	Leu	Phe	Ile		Gly	Tyr
S50	Ala	Pro		Asn	Leu	Ser	Ile	_	Gly	Glu	Tyr	Gln		Asn	Phe	His
865		850					855			_		860				_
## Record		Thr	Leu	Leu	Arg		Ile	Gln	Asp	Lys		Thr	Thr	Leu	Tyr	
Leu Asp Pro Ser Leu Val Glu Gln Val Phe Leu Asp Lys Thr Leu Asn 915					885	_			_	890					895	
Ala Ser Phe His Trp Leu Gly Ser Thr Tyr Gln Leu Val Asp Ile His 930 935 940 940 935 940 940 940 940 950 960 955 960 955 960 955 960 955 960 955 960 955 965 965 965 965 965 965 965 965 965	Thr	Met	Asp		Val	Leu	Val	Thr		Lys	Ala	Leu	Phe		Ser	Asn
930 935 940 Val Thr Glu Met Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser Ser Ser 945 950 950 960 Thr Gln His Phe Tyr Pro Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser 965 Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg 980 980 985 990 Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys 995 Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn 1010 1015 1020 Arg His His Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala	Leu	Asp		Ser	Leu	Val	Glu		Val	Phe	Leu	Asp		Thr	Leu	Asn
945 950 955 960 Thr Gln His Phe Tyr Pro Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser 965 970 970 Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg 980 985 990 Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys 995 1000 1005 Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn 1010 1015 1020 Arg His His Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala	Ala		Phe	His	Trp	Leu	_	Ser	Thr	Tyr	Gln		Val	Asp	Ile	His
965 970 975 Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg 980 985 990 Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys 995 1000 1005 Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn 1010 1015 1020 Arg His His Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala		Thr	Glu	Met	Glu	_	Ser	Val	Tyr	Gln		Thr	Ser	Ser	Ser	
980 985 990 Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys 995 1000 1005 Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn 1010 1015 1020 Arg His His Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala	Thr	Gln	His	Phe	_	Pro	Asn	Phe	Thr		Thr	Asn	Leu	Pro	_	Ser
995 1000 1005 Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn 1010 1015 1020 Arg His His Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala	Gln	Asp	ГÀЗ		Gln	Pro	Gly	Thr		Asn	Tyr	Gln	Arg		ГÀЗ	Arg
Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn 1010 1015 1020 Arg His His Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala	Asn	Ile		Asp	Ala	Leu	Asn			Phe	Arg	Asn			Ile	Lys
	Ser			Ser	Asp	Cys			Ser	Thr	Phe			Val	Pro	Asn
			His	Thr	Gly			Ser	Leu	Cys			Ser	Pro	Leu	

161

Arg Arg Val Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr 1045 1050 1055 Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val 1060 1065 1070 Leu Val Asp Gly Tyr Ser Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn 1075 1080 1085 Ser Asp Leu Pro Phe Trp Ala Val Ile Phe Ile Gly Leu Ala Gly Leu 1090 1095 1100 Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr Arg 1105 1110 1115 Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys Pro Gly 1125 1130 Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln 1140 1145

<210> 480 <211> 230 <212> PRT

<213> Homo sapiens

<400> 480

Met His Arg Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu 5 10 Gln Thr Leu Leu Gly Pro Met Phe Lys Asn Thr Ser Val Gly Leu Leu 25 Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Ser Glu Lys Asp Gly Ala 35 40 45 Ala Thr Gly Val Asp Ala Ile Cys Thr His Arg Leu Asp Pro Lys Ser 55 Pro Gly Val Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr 75 Asn Gly Ile Lys Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu 85 90 Tyr Val Asn Gly Phe Thr His Trp Ile Pro Val Pro Thr Ser Ser Thr 100 105 110 Pro Gly Thr Ser Thr Val Asp Leu Gly Ser Gly Thr Pro Ser Ser Leu 115 120 125 Pro Ser Pro Thr Thr Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn 135 140 Phe Thr Ile Thr Asn Leu Lys Tyr Glu Glu Asp Met His Cys Pro Gly 150 155 Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Ser Leu Leu Gly 165 170 Pro Met Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg 180 185 190 · Leu Thr Leu Leu Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly Val Asp 195 200 205 Ala Ile Cys Thr His Arg Leu Asp Pro Lys Ser Leu Glu Trp Thr Gly Ser Ser Tyr Thr Gly Ser 230

<210> 481

<211> 210

<212> PRT

<213> Homo sapiens

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<210> 483 <211> 438 <212> PRT <213> Homo sapiens

<400> 483															
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Leu	Gln	Tyr	Ser 20	Pro	Asp	Met	Gly	Lys 25	Gly	Ser	Ala	Thr	Phe 30	Asn	Ser
Thr	Glu	Gly 35	Val	Leu	Gln	His	Leu 40	Leu	Arg	Pro	Leu	Phe 45	Gln	Lys	Ser
Ser	Met 50	Gly	Pro	Phe	Tyr	Leu 55	Gly	Cys	Gln	Leu	Ile 60	Ser	Leu	Arg	Pro
Glu 65	Lys	Asp	Gly	Ala	Ala 70	Thr	Gly	Val	Asp	Thr 75	Thr	Cys	Thr	Tyr	His 80
Pro	Asp	Pro	Val	Gly 85	Pro	Gly	Leu	Asp	Ile 90	Gln	Gln	Leu	Tyr	Trp 95	Glu
Leu	Ser	Gln	Leu 100	Thr	His	Gly	Val	Thr 105	Gln	Leu	Gly	Phe	Tyr 110	Val	Leu
_	-	115	Ser				120	_	-			125			
	130	_	Glu	_		135					140		_		
145			Asp		150				_	155				_	160
			Lys	165					170					175	
		_	Phe 180	-				185				_	190		
		195	Lys				200					205			
	210		Phe		_	215					220			-	
225			Tyr		230					235					240
			Gln	245					250					255	
			Ile 260					265			_		270		
		275	Asn	-		_	280	_	_			285	_		
	290		Phe			295					300				
305			Thr		310					315					320
			Cys	325					330		_		_	335	
			340					345				_	350		Leu
		355				_	360					365	_	_	Ser
	370		Asn			375					380				
385			Leu		390					395					400
				405					410					415	Gly
			420			GIN	cys	425	стХ	Tyr	туr	GIN	430	HIS	Leu
nsp	neu	435	Asp	neu	GIII										

164

PCT/US01/22635

WO 02/06317

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<210> 484
<211> 216
<212> PRT
<213> Homo sapiens
<400> 484
Met Thr Leu Lys Ser Trp Ala Pro Thr Pro Trp Thr Gly Thr Val Ser
1 5
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Met Ser Met Val Ser Pro Ile Arg Ala Leu Cys Pro Pro Pro Ala Leu
20
                          25
Leu Gly Pro Pro Gln Trp Ile Ser Glu Pro Gln Trp Thr Pro Ser Ser
                       40
Leu Ser Ser Pro Thr Ile Met Ala Ala Gly Pro Leu Leu Val Pro Phe
                    55
Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr Gly Glu Asp Met Gly
                                 75
His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly
            85
                           90
Leu Leu Gly Pro Ile Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser
 100 105 110
Gly Cys Arg Leu Thr Ser Leu Arg Ser Lys Lys Asp Gly Ala Ala Thr
     115 120 125
Gly Val Asp Ala Ile Cys Ile His His Leu Asp Pro Lys Ser Pro Gly
   130 . 135
Leu Asn Arg Glu Arg Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Gly
               150 155 160
Ile Lys Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val
             165
                             170
Asn Gly Phe Thr His Arg Thr Ser Val Pro Thr Thr Ser Thr Pro Gly
       180 185
Thr Ser Thr Val Tyr Trp Ala Thr Thr Gly Thr Pro Ser Ser Leu Pro
 195 200 205
Ala Thr Gln Ser Leu Ala Leu Ser
   210
<210> 485
<211> 268
<212> PRT
<213> Homo sapiens
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                             10
Ser Gly Thr Pro Ser Ser Ser Pro Ser Pro Thr Thr Ala Gly Pro Leu
                          25
Leu Met Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr Glu
                       40
Glu Asp Met Arg Arg Thr Gly Ser Arg Lys Phe Asn Thr Met Glu Ser
                   55
                             60
Val Leu Gln Gly Leu Leu Lys Pro Leu Phe Lys Asn Thr Ser Val Gly
             70
                        75
Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Lys Lys Asp
                           90
            85
Gly Ala Ala Thr Gly Val Asp Ala Ile Cys Thr His Arg Leu Asp Pro
          100
                           105
```

165

Lys Ser Pro Gly Leu Asn Arg Glu Gln Leu Tyr Trp Glu Leu Ser Lys 115 120 Leu Thr Asn Asp Ile Glu Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn 135 Ser Leu Tyr Val Asn Gly Phe Thr His Gln Ser Ser Val Ser Thr Thr 145 150 155 Ser Thr Pro Gly Thr Ser Thr Val Asp Leu Arg Thr Ser Val Asp Ser 165 170 175 Ile Leu Pro Leu Gln Pro His Asn Tyr Gly Cys Trp Pro Ser Pro Gly 180 185 Thr Ile His Pro Gln Leu His His Gln Pro Ala Val Trp Gly Gly 200 His Gly Ser Pro Trp Leu Gln Glu Val Gln His His Arg Glu Gly Pro 210 215 Ala Gly Ser Ala Trp Ser His Ile Gln Glu His Gln Cys Trp Pro Ser 225 230 235 Val Leu Trp Leu Gln Thr Asp Leu Ser Gln Val Gln Glu Gly Trp Ser 250 245 Ser His Trp Ser Gly Cys His Leu His Pro Ser Ser

<210> 486

<211> 304

<212> PRT

<213> Homo sapiens

<400> 486

Met Gln His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu 10 Gln Gly Leu Leu Arg Pro Leu Phe Lys Asn Thr Ser Val Gly Pro Leu 25 Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Glu 40 Ala Thr Gly Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Thr Gly 55 Pro Gly Leu Asp Arg Glu Gln Leu Tyr Leu Glu Leu Ser Gln Leu Thr 70 75 His Ser Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser Leu 85 90 Tyr Val Asn Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Thr 105 Gly Val Val Ser Glu Glu Pro Phe Thr Leu Asn Phe Thr Ile Asn Asn 120 Leu Arg Tyr Met Ala Asp Met Gly Gln Pro Gly Ser Leu Lys Phe Asn 135 140 Ile Thr Asp Asn Val Met Lys His Leu Leu Ser Pro Leu Phe Gln Arg 150 155 Ser Ser Leu Gly Ala Arg Tyr Thr Gly Cys Arg Val Ile Ala Leu Arg 170 Ser Val Lys Asn Gly Ala Glu Thr Arg Val Asp Leu Leu Cys Thr Tyr 185 Leu Gln Pro Leu Ser Gly Pro Gly Leu Pro Ile Lys Gln Val Phe His 200 Glu Leu Ser Gln Gln Thr His Gly Ile Thr Arg Leu Gly Pro Tyr Ser 210 215 220 Leu Asp Lys Asp Ser Leu Tyr Leu Asn Gly Tyr Asn Glu Pro Gly Pro 230 235

166

Asp Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr Phe Leu Pro Pro 245 250 255 Leu Ser Glu Ala Thr Thr Ala Met Gly Tyr His Leu Lys Thr Leu Thr 265 Leu Asn Ser His Leu Gln Ser Pro Val Phe Thr Arg Tyr Gly Gln Gly 280 285 Leu Lys Val His Ser Ile His Arg Gly Gly Ser Phe Ser Asn Trp Ser

<210> 487

<211> 294

<212> PRT

<213> Homo sapiens

<400> 487 Met Thr Asn Gly Ile Lys Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn 5 10 Ser Leu Tyr Val Asn Gly Phe Thr His Arg Ser Ser Gly Leu Thr Thr 25 Ser Thr Pro Trp Thr Ser Thr Val Asp Leu Gly Thr Ser Gly Thr Pro 40 Ser Pro Val Pro Ser Pro Thr Thr Ala Gly Pro Leu Leu Val Pro Phe 50 . 55 Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met His 70 75 Arg Pro Gly Ser Arg Lys Phe Asn Ala Thr Glu Arg Val Leu Gln Gly 90 85 Leu Leu Ser Pro Ile Phe Lys Asn Ser Ser Val Gly Pro Leu Tyr Ser 105 Gly Cys Arg Leu Thr Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr 120 Gly Met Asp Ala Val Cys Leu Tyr His Pro Asn Pro Lys Arg Pro Gly 135 140 Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Asn 150 155 Ile Thr Glu Leu Gly Pro Tyr Ser Leu Asp Arg Asp Ser Leu Tyr Val 165 170 Asn Gly Phe Thr His Gln Asn Ser Val Pro Thr Thr Ser Thr Pro Gly 180 185 190 . Thr Ser Thr Val Tyr Trp Ala Thr Thr Gly Thr Pro Ser Ser Phe Pro 200 Gly His Thr Glu Pro Gly Pro Leu Leu Ile Pro Phe Thr Phe Asn Phe 215 220 Thr Ile Thr Asn Leu His Tyr Glu Glu Asn Met Gln His Pro Gly Ser 230 235 Arg Lys Phe Asn Ala Thr Glu Arg Val Leu Gln Gly Leu Leu Ser Pro 250 245 Ile Phe Lys Asn Ser Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu 265 270 Thr Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Met Asp Ala 275 280 Val Cys Leu Tyr Arg Pro

290

<210> 488 <211> 233

<212> PRT <213> Homo sapiens

<400> 488

Ser Leu Val Glu Gln Val Phe Leu Asp Lys Thr Leu Asn Ala Ser Phe 10 His Trp Leu Gly Ser Thr Tyr Gln Leu Val Asp Ile His Val Thr Glu Met Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser Ser Ser Thr Gln His 40 45 Phe Tyr Leu Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser Gln Asp Lys 55 Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg Asn Ile Glu 70 Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys Ser Tyr Phe 85 90 Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn Arg His His 100 105 110 Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala Arg Arg Val 120 125 Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr Arg Asn Gly 130 135 140 Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val Leu Val Asp 150 155 Gly Tyr Phe Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn Ser Asp Leu 170 Pro Phe Trp Ala Val Ile Leu Ile Gly Leu Ala Gly Leu Leu Gly Leu 180 185 Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr Arg Arg Arg Lys 195 200 205 Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys Pro Gly Tyr Tyr Gln 210 215 Ser His Leu Asp Leu Glu Asp Leu Gln

<210> 489

<211> 178

<212> PRT

<213> Homo sapiens

<400> 489

Ser Leu Val Glu Gln Val Phe Leu Asp Lys Thr Leu Asn Ala Ser Phe 10 His Trp Leu Gly Ser Thr Tyr Gln Leu Val Asp Ile His Val Thr Glu 25 Met Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser Ser Ser Thr Gln His 40 Phe Tyr Leu Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser Gln Asp Lys 60 50 55 Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg Asn Ile Glu 70 75 Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys Ser Tyr Phe 85 90 Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn Arg His His 105 Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala Arg Arg Val 115 120

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Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr Arg Asn Gly
 130 135 140
Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val Leu Val Asp
                             155
                150
Gly Tyr Phe Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn Ser Asp Leu
              165 170
Pro Phe
<210> 490
<211> 15
<212> PRT
<213> Homo sapiens
<400> 490
Thr Cys Gly Met Arg Arg Thr Cys Ser Thr Leu Ala Pro Gly Ser
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<210> 491
<211> 15
<212> PRT
<213> Homo sapiens
<400> 491
Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Thr Ala Thr
             5
                               10
<210> 492
<211> 15
<212> PRT
<213> Homo sapiens
Asp Gly Thr Ala Thr Gly Val Asp Ala Ile Cys Thr His His Pro
              5
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<210> 493
<211> 15
<212> PRT
<213> Homo sapiens
Cys Thr His His Pro Asp Pro Lys Ser Pro Arg Leu Asp Arg Glu
               5
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Arg Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr
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1
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<211> 15
<212> PRT
<213> Homo sapiens
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<210> 496
<211> 15
<212> PRT
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Ser Val Ser Thr Thr Ser Thr Pro Gly Thr Pro Thr Tyr Val Leu
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<210> 497
<211> 15
<212> PRT
<213> Homo sapiens
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Leu Arg Pro Glu Lys Asp Gly Glu Ala Thr Gly Val Asp Ala Ile
<210> 498
<211> 15
<212> PRT
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Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Gln Leu Tyr Leu Glu
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<212> PRT
<213> Homo sapiens
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Leu Asp Arg Asp Ser Leu Tyr Val Asn Gly Phe Thr His Arg Ser
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Gly Pro Tyr Ser Leu Asp Lys Asp Ser Leu Tyr Leu Asn Gly Tyr
1 5 10
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<211> 15
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Tyr Leu Asn Gly Tyr Asn Glu Pro Gly Pro Asp Glu Pro Pro Thr
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<211> 15
<212> PRT
<213> Homo sapiens
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Ala Thr Phe Asn Ser Thr Glu Gly Val Leu Gln His Leu Leu Arg
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<211> 15
<212> PRT
<213> Homo sapiens
Gln Leu Ile Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly
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<210> 504
<211> 15
<212> PRT
<213> Homo sapiens
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Gly Ala Ala Thr Gly Val Asp Thr Thr Cys Thr Tyr His Pro Asp
           5
                          10
<210> 505
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<212> PRT
<213> Homo sapiens
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Thr Tyr His Pro Asp Pro Val Gly Pro Gly Leu Asp Ile Gln Gln
              5
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<210> 506
<211> 15
<212> PRT
<213> Homo sapiens
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Leu Asp Ile Gln Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His
<210> 507
<211> 15
<212> PRT
<213> Homo sapiens
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His Ile Val Asn Trp Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser
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<211> 15
<212> PRT
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Asp Pro Thr Ser Ser Glu Tyr Ile Thr Leu Leu Arg Asp Ile Gln
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<211> 15
<212> PRT
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Leu Arg Asp Ile Gln Asp Lys Val Thr Thr Leu Tyr Lys Gly Ser
<210> 510
<211> 15
<212> PRT
<213> Homo sapiens
Leu Tyr Lys Gly Ser Gln Leu His Asp Thr Phe Arg Phe Cys Leu
              5
                   10
<210> 511
<211> 15
<212> PRT
<213> Homo sapiens
<400> 511
Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg
<210> 512
<211> 450
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<212> DNA
<213> Homo sapiens
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acttcaccat ctccaatctc cagtattcac cagatatggg caagggctca gctacattca 180
actocaccga gggggtcctt cagcacctgc tcagaccctt gttccagaag agcagcatgg 240
gccccttcta cttgggttgc caactgatct ccctcaggcc tgagaaggat ggggcagcca 300
ctggtgtgga caccacctgc acctaccacc ctgaccctgt gggccccggg ctggacatac 360
agcagettta etgggagetg agteagetga eccatggtgt cacecaactg ggettetatg 420
tcctggacag ggatagcctc ttcatcaatg
<210> 513
<211> 402
<212> DNA
<213> Homo sapiens
<400> 513
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tcacactgaa cttcaccatc aacaacctgc gctacatggc ggacatgggc caacccggct 120
ccctcaagtt caacatcaca gacaacgtca tgaagcacct gctcagtcct ttgttccaga 180
ggagcagcct gggtgcacgg tacacaggct gcagggtcat cgcactaagg tctgtgaaga 240
acggtgctga gacacgggtg gacctcctct gcacctacct gcagcccctc agcggcccag 300
gtctgcctat caagcaggtg ttccatgagc tgagccagca gacccatggc atcacccggc 360
tgggccccta ctctctggac aaagacagcc tctaccttaa cg
<210> 514
<211> 465
<212> DNA
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<212> DNA
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<212> DNA
<213> Homo sapiens
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<211> 468
<212> DNA
<213> Homo sapiens
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183

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<212> DNA
<213> Homo sapiens
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PCT/US01/22635

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<213> Homo sapiens
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<213> Homo sapiens .
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<211> 450
<212> DNA
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<222> 406,742,801
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<400> 568
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187

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      321, 350, 387, 412, 414, 415, 422, 423, 451
<223> n = A, T, C or G
<400> 570
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tgggaacctc wgggactcca tcctccctcc cyrgccccac agctgctggc cctctcctgr 120
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<213> Homo sapiens
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<221> variant
<222> 69,107,110
<223> Xaa = Any amino acid
<400> 571
His Pro Gln Leu Glu Gln Gln Pro Gln Ser His Ser Trp Cys His Ser
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Pro Ser Thr Ser Thr His His Gln Pro Ala Val Arg Gly Gly His Ala
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Ala Pro Gly Ser Arg Lys Phe Asn Ala His Arg Glu Arg Thr Ala Gly

PCT/US01/22635

Ser Cys Ser Asn Pro Arg Ser Gly Ile Ala Val Trp Asn Thr Ser Ile

Gln Ala Ala Asp Xaa Pro His Ser Gly Gln Arg Arg Ile Ala Gln Pro

Arg Gln Trp Met Pro Ser Ala His Ile Ala Leu Thr Leu Lys Thr Ser

Asp Trp Thr Glu Ser Asp Cys Thr Gly Ser Xaa Ala Ile Xaa Gln Met 100 105

Ala Ser Arg Ser Trp Ala Pro Thr Pro Trp Thr Gly Thr Val Ser Met 120

Ser Met 130

<210> 572

WO 02/06317

<211> 130

<212> PRT

<213> Homo sapiens

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<221> variant

<222> 1,58,78,92,94

<223> Xaa = Any amino acid

<400> 572

Xaa Ile Pro Ser Ser Asn Ser Ser His Ser Pro Ile His Gly Ala Ile 10

His Pro Gln Leu Gln Leu Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met

Arg His Leu Val Pro Gly Ser Ser Thr Arg Thr Glu Arg Glu Leu Gln

Gly Arg Ala Gln Thr Leu Asp Gln Glu Xaa Gln Ser Gly Ile Pro Leu

Phe Arg Leu Gln Thr Ser Leu Thr Gln Ala Arg Glu Gly Xaa Leu Ser

His Gly Ser Gly Cys His Leu His Thr Ser Pro Xaa Pro Xaa Arg Pro

Arg Thr Gly Gln Arg Ala Thr Val Leu Gly Ala Glu Gln Ser Asp Lys 105

Trp His Pro Gly Ala Gly Pro Leu His Pro Gly Pro Glu Gln Ser Leu 120 125

Cys Gln

191

130

<210> 573

<211> 130

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 1,54

<223> Xaa = Any amino acid

<400> 573

Xaa Ser Pro Ala Arg Thr Ala Ala Thr Val Pro Phe Met Val Pro Phe
5 10 15

Thr Leu Asn Phe Asn Ser Ser Pro Thr Cys Ser Thr Arg Arg Thr Cys
20 25 30

Gly Thr Trp Phe Gln Glu Val Gln Arg Ala Gln Arg Glu Asn Cys Arg 35 40 45

Val Val Leu Lys Pro Xaa Ile Arg Asn Ser Ser Leu Glu Tyr Leu Tyr 50 55 60

Ser Gly Cys Arg Leu Ala Ser Leu Arg Pro Glu Lys Asp Ser Ser Ala 65 70 75 80

Thr Ala Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Glu Asp Leu 85 90 95

Gly Leu Asp Arg Glu Arg Leu Tyr Trp Glu Leu Ser Asn Leu Thr Asn 100 105 110

Gly Ile Gln Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr 115 120 125

Val Asn 130

<210> 574

<211> 156

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 101

<223> Xaa = Any amino acid

<400> 574

Gly Phe Thr His Arg Ser Ser Met Pro Thr Thr Ser Thr Pro Gly Thr

Ser Thr Val Asp Val Gly Thr Ser Gly Thr Pro Ser Ser Ser Pro Ser

Pro Thr Thr Ala Gly Pro Leu Leu Met Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met Arg Arg Thr Gly Ser Arg 50 55 60

Lys Phe Asn Thr Met Glu Ser Val Leu Gln Gly Leu Leu Lys Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Xaa Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg Glu Gln 115 120 125

Leu Tyr Trp Glu Leu Ser Lys Leu Thr Asn Asp Ile Glu Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn 145 150 155

<210> 575

<211> 158

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 103

<223> Xaa = Any amino acid

<400> 575

Gly Phe Thr His Gln Ser Ser Val Ser Thr Thr Ser Thr Pro Gly Thr 5 10 15

Ser Thr Val Asp Leu Arg Thr Ser Val Thr Pro Ser Ser Leu Ser Ser 20 25 30

Pro Thr Ile Met Ala Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn 35 40 45

Phe Thr Ile Thr Asn Leu Gln Tyr Gly Glu Asp Met Gly His Pro Gly 50 55 60

Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly 65 70 75 80

Pro Ile Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg 85 90 . 95

Leu Thr Ser Leu Arg Ser Xaa Lys Asp Gly Ala Ala Thr Gly Val Asp 100 105 110

Ala Ile Cys Ile His His Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg 115 120 125

Glu Arg Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Gly Ile Lys Glu 130 135 140

Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn 145 150 155

<210> 576

<211> 122

<212> PRT

<213> Homo sapiens

<400> 576

Ala Ala Gly Pro Leu Leu Val Leu Phe Thr Leu Asn Phe Thr Ile Thr 5 10 15

Asn Leu Lys Tyr Glu Glu Asp Met His Arg Pro Gly Ser Arg Lys Phe 20 25 30

Asn Thr Thr Glu Arg Val Leu Gln Thr Leu Arg Gly Pro Met Phe Lys 35 40 45

Asn Thr Ser Gly Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu 50 60

Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys Thr 65 70 75 80

His Arg Leu Asp Pro Lys Ser Pro Gly Val Asp Arg Glu Gln Leu Tyr

Trp Glu Leu Ser Gln Leu Thr Asn Gly Ile Lys Glu Leu Gly Pro Tyr 100 105 110

Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn

<210> 577

<211> 156

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 11,106,151

<223> Xaa = Any amino acid

<400> 577

Gly Phe Thr His Arg Thr Ser Val Pro Thr Xaa Ser Thr Pro Gly Thr

Ser Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Phe Ser Leu Pro Ser 20 25 30

Pro Ala Thr Ala Gly Pro Leu Leu Val Leu Phe Thr Leu Asn Phe Thr 35 40 45

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Thr Leu Leu Gly Pro Met 65 70 75 80

Phe Lys Asn Thr Ser Val Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Ser Glu Lys Asp Gly Ala Xaa Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Val Asp Arg Glu Gln
115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Gly Ile Lys Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Xaa Ser Leu Tyr Val Asn 145 150 155

<210> 578

<211> 155

<212> PRT

<213> Homo sapiens

<400> 578

Ser Thr Val Asp Leu Gly Ser Gly Thr Pro Ser Ser Leu Pro Ser Pro 20 25 30

Thr Thr Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile 35 40 45

Thr Asn Leu Gln Tyr Glu Glu Asp Met His His Pro Gly Ser Arg Lys
50 55 60

Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly Pro Met Phe 65 70 75 80

Lys Asn Thr Ser Val Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr Leu 85 90 95

Leu Arg Pro Glu Lys Asn Gly Ala Ala Thr Gly Met Asp Ala Ile Cys 100 105 110

Ser His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg Glu Gln Leu 115 120 125

Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Ile Lys Glu Leu Gly Pro 130 135 140

Tyr Thr Leu Asp Arg His Ser Leu Tyr Val Asn 150 <210> 579 <211> 155 <212> PRT <213> Homo sapiens <220> <221> variant <222> 52,138 <223> Xaa = Any amino acid <400> 579 Gly Phe Thr His Trp Ile Pro Val Pro Thr Ser Ser Thr Pro Gly Thr Ser Thr Val Asp Leu Gly Ser Gly Thr Pro Ser Ser Leu Pro Ser Pro Thr Thr Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Xaa Tyr Glu Glu Asp Met His Cys Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Ser Leu Leu Gly Pro Met Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys 105 Thr His Arg Leu Asp Pro Lys Ser Pro Gly Val Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Xaa Ile Lys Glu Leu Gly Pro Tyr Thr Leu Asp Ser Asn Ser Leu Tyr Val Asn 150 <210> 580 <211> 156 <212> PRT <213> Homo sapiens <220> <221> variant <222> 23 <223> Xaa = Any amino acid <400> 580 Gly Phe Thr His Gln Thr Ser Ala Pro Asn Thr Ser Thr Pro Gly Thr

WO 02/06317 PCT/US01/22635

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197

115 120 125 Leu Tyr Trp Gln Leu Ser Gln Met Thr Asn Gly Ile Lys Glu Leu Gly 130 135 Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn 150 <210> 582 <211> 156 <212> PRT <213> Homo sapiens <220> <221> variant <222> 151 <223> Xaa = Any amino acid <400> 582 Gly Phe Thr His Arg Ser Ser Gly Leu Thr Thr Ser Thr Pro Trp Thr Ser Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Ser Pro Val Pro Ser Pro Thr Thr Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met His Arg Pro Gly Ser Arg Lys Phe Asn Ala Thr Glu Arg Val Leu Gln Gly Leu Leu Ser Pro Ile Phe Lys Asn Ser Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Met Asp Ala Val Cys Leu Tyr His Pro Asn Pro Lys Arg Pro Gly Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Asn Ile Thr Glu Leu Gly Pro Tyr Ser Leu Asp Arg Xaa Ser Leu Tyr Val Asn 150

<210> 583 <211> 156 <212> PRT <213> Homo sapiens <220>

<221> variant

198

<222> 109,114,117,128,139 <223> Xaa = Any amino acid

<400> 583

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Ser Thr Val Tyr Trp Ala Thr Thr Gly Thr Pro Ser Ser Phe Pro Gly 20 25 30

His Thr Glu Pro Gly Pro Leu Leu Ile Pro Phe Thr Phe Asn Phe Thr 35 40 45

Ile Thr Asn Leu His Tyr Glu Glu Asn Met Gln His Pro Gly Ser Arg 50 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Thr Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Gln Glu Ala Ala Thr Gly Xaa Asp Thr Ile
100 105 110

Cys Xaa His Arg Xaa Asp Pro Ile Gly Pro Gly Leu Asp Arg Glu Xaa 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Xaa Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

<210> 584

<211> 156

<212> PRT

<213> Homo sapiens

<400> 584

Gly Phe Asn Pro Trp Ser Ser Val Pro Thr Thr Ser Thr Pro Gly Thr
5 10 15

Ser Thr Val His Leu Ala Thr Ser Gly Thr Pro Ser Ser Leu Pro Gly
20 25 30

His Thr Ala Pro Val Pro Leu Leu Ile Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu His Tyr Glu Glu Asn Met Gln His Pro Gly Ser Arg 50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Lys Pro Leu 65 70 75 80

Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys His Gly Ala Ala Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr Leu Arg Leu Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Arg 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Ser Val Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

<210> 585

<211> 156

<212> PRT

<213> Homo sapiens

<400> 585

Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Ile Pro Gly Thr 5 10 15

Ser Ala Val His Leu Glu Thr Ser Gly Thr Pro Ala Ser Leu Pro Gly 20 25 30

His Thr Ala Pro Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40

Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met Arg His Pro Gly Ser Arg 50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Lys Pro Leu 65 70 75 80

Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Arg Gly Ala Ala Thr Gly Val Asp Thr Ile 100 105 110

Cys Thr His Arg Leu Asp Pro Leu Asn Pro Gly Leu Asp Arg Glu Gln
115 120 125

Leu Tyr Trp Glu Leu Ser Lys Leu Thr Cys Gly Ile Ile Glu Leu Gly 130 135 140

Pro Tyr Leu Leu Asp Arg Gly Ser Leu Tyr Val Asn 145 150 155

<210> 586

<211> 156

<212> PRT

<213> Homo sapiens

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<221> variant

<222> 151,156 <223> Xaa = Any amino acid

<400> 586

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Ser Thr Val His Leu Gly Thr Ser Glu Thr Pro Ser Ser Leu Pro Arg 20 25 30

Pro Ile Val Pro Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Ala Met Arg His Pro Gly Ser Arg
50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Ile Gly Pro Leu Tyr Ser Ser Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asp Lys Ala Ala Thr Arg Val Asp Ala Ile 100 105 110

Cys Thr His His Pro Asp Pro Gln Ser Pro Gly Leu Asn Arg Glu Gln 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Ile Thr Glu Leu Gly 130 135 140

<210> 587

<211> 156

<212> PRT

<213> Homo sapiens

<400> 587

Gly Phe Thr His Trp Ser Pro Ile Pro Thr Thr Ser Thr Pro Gly Thr 10 15

Ser Ile Val Asn Leu Gly Thr Ser Gly Ile Pro Pro Ser Leu Pro Glu 20 25 30

Thr Thr Ala Thr Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40 45

Lys Phe Asn Ile Thr Glu Ser Val Leu Gln Gly Leu Leu Lys Pro Leu 65 70 75 80

Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asp Gly Val Ala Thr Arg Val Asp Ala Ile 100 105 110

Cys Thr His Arg Pro Asp Pro Lys Ile Pro Gly Leu Asp Arg Gln Gln
115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly 130 135

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

<210> 588

<211> 156

<212> PRT

<213> Homo sapiens

<400> 588

Gly Phe Thr Gln Arg Ser Ser Val Pro Thr Thr Ser Thr Pro Gly Thr
5 10 15

Phe Thr Val Gln Pro Glu Thr Ser Glu Thr Pro Ser Ser Leu Pro Gly 20 25 30

Pro Thr Ala Thr Gly Pro Val Leu Leu Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Ile Asn Leu Gln Tyr Glu Glu Asp Met His Arg Pro Gly Ser Arg 50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Met Pro Leu
65 70 75 80

Phe Lys Asn Thr Ser Val Ser Ser Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Arg Val Asp Ala Val
100 105 110

Cys Thr His Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Arg 115 120 125

Leu Tyr Trp Lys Leu Ser Gln Leu Thr His Gly Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg His Ser Leu Tyr Val Asn 145 150 155

<210> 589

<211> 156

<212> PRT

<213> Homo sapiens

<400> 589

Gly Phe Thr His Gln Ser Ser Met Thr Thr Thr Arg Thr Pro Asp Thr

202

5 10 15 Ser Thr Met His Leu Ala Thr Ser Arg Thr Pro Ala Ser Leu Ser Gly 25 Pro Thr Thr Ala Ser Pro Leu Leu Val Leu Phe Thr Ile Asn Phe Thr Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met His His Pro Gly Ser Arg 55 Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Val Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Lys Lys Asp Gly Ala Ala Thr Lys Val Asp Ala Ile Cys Thr Tyr Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly 135 Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn <210> 590 <211> 156 <212> PRT <213> Homo sapiens <220> <221> variant <222> 145 <223> Xaa = Any amino acid <400> 590 Gly Phe Thr Gln Arg Ser Ser Val Pro Thr Thr Ser Ile Pro Gly Thr Pro Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Val Ser Lys Pro Gly Pro Ser Ala Ala Ser Pro Leu Leu Val Leu Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met Gln His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Ser Leu 75 Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr

203

Leu Leu Arg Pro Glu Lys Asp Gly Thr Ala Thr Gly Val Asp Ala Ile
100 105 110

Cys Thr His His Pro Asp Pro Lys Ser Pro Arg Leu Asp Arg Glu Gln
115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Asn Ile Thr Glu Leu Gly 130 135 140

Xaa Tyr Ala Leu Asp Asn Asp Ser Leu Phe Val Asn 145 150 155

<210> 591

<211> 155

<212> PRT

<213> Homo sapiens

<400> 591

Gly Phe Thr His Arg Ser Ser Val Ser Thr Thr Ser Thr Pro Gly Thr 5 $$ 10 15

Pro Thr Val Tyr Leu Gly Ala Ser Lys Thr Pro Ala Ser Ile Phe Gly 20 25 30

Pro Ser Ala Ala Ser His Leu Leu Ile Leu Phe Thr Leu Asn Phe Thr 35 40

Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met Trp Pro Gly Ser Arg Lys 50 60

Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Leu Phe 65 70 75 80

Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu 85 90 95

Leu Arg Pro Glu Lys Asp Gly Glu Ala Thr Gly Val Asp Ala Ile Cys 100 105 110

Thr His Arg Pro Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Gln Leu 115 120 125

Tyr Leu Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly Pro 130 135 140

Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

<210> 592

<211> 134

<212> PRT

<213> Homo sapiens

<400> 592

Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Thr Gly Val Val

204

10 15 Ser Glu Glu Pro Phe Thr Leu Asn Phe Thr Ile Asn Asn Leu Arg Tyr Met Ala Asp Met Gly Gln Pro Gly Ser Leu Lys Phe Asn Ile Thr Asp Asn Val Met Lys His Leu Leu Ser Pro Leu Phe Gln Arg Ser Ser Leu Gly Ala Arg Tyr Thr Gly Cys Arg Val Ile Ala Leu Arg Ser Val Lys Asn Gly Ala Glu Thr Arg Val Asp Leu Leu Cys Thr Tyr Leu Gln Pro Leu Ser Gly Pro Gly Leu Pro Ile Lys Gln Val Phe His Glu Leu Ser Gln Gln Thr His Gly Ile Thr Arg Leu Gly Pro Tyr Ser Leu Asp Lys Asp Ser Leu Tyr Leu Asn 130 <210> 593 <211> 150 <212> PRT <213> Homo sapiens <220> <221> variant <222> 7 <223> Xaa = Any amino acid Gly Tyr Asn Glu Pro Gly Xaa Asp Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr Phe Leu Pro Pro Leu Ser Glu Ala Thr Thr Ala Met Gly Tyr His Leu Lys Thr Leu Thr Leu Asn Phe Thr Ile Ser Asn Leu Gln Tyr Ser Pro Asp Met Gly Lys Gly Ser Ala Thr Phe Asn Ser Thr Glu Gly Val Leu Gln His Leu Leu Arg Pro Leu Phe Gln Lys Ser Ser Met Gly Pro Phe Tyr Leu Gly Cys Gln Leu Ile Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Thr Thr Cys Thr Tyr His Pro Asp

105

Pro Val Gly Pro Gly Leu Asp Ile Gln Gln Leu Tyr Trp Glu Leu Ser 115 120 125

Gln Leu Thr His Gly Val Thr Gln Leu Gly Phe Tyr Val Leu Asp Arg 130 135 140

Asp Ser Leu Phe Ile Asn 145 150

<210> 594

<211> 318

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 136,248,268

<223> Xaa = Any amino acid

<400> 594

Gly Tyr Ala Pro Gln Asn Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn 5 10 15

Phe His Ile Val Asn Trp Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser 20 25 30

Glu Tyr Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys Val Thr Thr Leu $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$

Tyr Lys Gly Ser Gln Leu His Asp Thr Phe Arg Phe Cys Leu Val Thr 50 55 60

Asn Leu Thr Met Asp Ser Val Leu Val Thr Val Lys Ala Leu Phe Ser 65 70 75 80

Ser Asn Leu Asp Pro Ser Leu Val Glu Gln Val Phe Leu Asp Lys Thr 85 90 95

Leu Asn Ala Ser Phe His Trp Leu Gly Ser Thr Tyr Gln Leu Val Asp 100 105 110

Ile His Val Thr Glu Met Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser 115 120 125

Ser Ser Thr Gln His Phe Tyr Xaa Asn Phe Thr Ile Thr Asn Leu Pro 130 135 140

Tyr Ser Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn 145 150 155 160

Lys Arg Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser 165 170 . 175

Ile Lys Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val 180 185 190

206

Pro Asn Arg His His Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro 195 200 205 Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg 215 Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Xaa Pro Asn Arg Asn Glu Pro Leu Thr 250 Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Xaa Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr 280 Thr Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys 295 Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln 310 315 <210> 595 <211> 3451 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> 177, 335, 523, 618, 663, 875, 961, 1001, 1441, 1555, 1560, 1563, 1574, 1585, 2065, 2070, 2683, 2990, 3269, 3381, 3401 <223> Xaa = Any Amino Acid <400> 595 Ile Arg Asn Ser Ser Leu Glu Tyr Leu Tyr Ser Gly Cys Arg Leu Ala 10 Ser Leu Arg Pro Glu Lys Asp Ser Ser Ala Thr Ala Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Glu Asp Leu Gly Leu Asp Arg Glu Arg 40 Leu Tyr Trp Glu Leu Ser Asn Leu Thr Asn Gly Ile Gln Glu Leu Gly 55 Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn Gly Phe Thr His 75 70 Arg Ser Ser Met Pro Thr Thr Ser Thr Pro Gly Thr Ser Thr Val Asp 85 90 Val Gly Thr Ser Gly Thr Pro Ser Ser Ser Pro Ser Pro Thr Thr Ala 105 Gly Pro Leu Leu Met Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu 120 125 Gln Tyr Glu Glu Asp Met Arg Arg Thr Gly Ser Arg Lys Phe Asn Thr

135

150

Met Glu Ser Val Leu Gln Gly Leu Leu Lys Pro Leu Phe Lys Asn Thr

Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro

155

140

207

	_	_		165					170			_		175	_
хаа	Lys	Asp	GLy 180	Ala	Ala	Thr	GTA	Val 185	Asp	Ala	ile	Cys	190	HIS	Arg
Leu	Asp	Pro 195	Lys	Ser	Pro	Gly	Leu 200	Asn	Arg	Glu	Gln	Leu 205	Tyr	Trp	Glu
Leu	Ser 210	Lys	Leu	Thr	Asn	Asp 215	Ile	Glu	Glu	Leu	Gly 220	Pro	Tyr	Thr	Leu
Asp 225	Arg	Asn	Ser	Leu	Tyr 230	Val	Asn	Gly	Phe	Thr 235	His	Gln	Ser	Ser	Val 240
Ser	Thr	Thr	Ser	Thr 245	Pro	Gly	Thr	Ser	Thr 250	Val	Asp	Leu	Arg	Thr 255	Ser
Val	Thr	Pro	Ser 260	Ser	Leu	Ser	Ser	Pro 265	Thr	Ile	Met	Ala	Ala 270	Gly	Pro
Leu	Leu	Val 275	Pro	Phe	Thr	Leu	Asn 280	Phe	Thr	Ile	Thr	Asn 285	Leu	Gln	Tyr
Gly	Glu 290	Asp	Met	Gly	His	Pro 295	Gly	Ser	Arg	Lys	Phe 300	Asn	Thr	Thr	Glu
Arg 305	Val	Leu	Gln	Gly	Leu 310	Leu	Gly	Pro	Ile	Phe 315	Lys	Asn	Thr	Ser	Val 320
_	Pro		-	325	_		_		330					335	-
	Gly		340					345					350		
Pro	Гуѕ	Ser 355	Pro	Gly	Leu	Asn	Arg 360	Glu	Arg	Leu	Tyr	Trp 365	Glu	Leu	Ser
Gln	Leu 370	Thr	Asn	Gly	Ile	Lys 375	Glu	Leu	Gly	Pro	Tyr 380	Thr	Leu	Asp	Arg
Asn 385	Ser	Leu	Tyr	Val	Asn 390	Ala	Ala	Gly	Pro	Leu 395	Leu	Val	Leu	Phe	Thr 400
	Asn			405					410					415	_
	Gly		420					425					430		
	Gly	435					440					445			
-	Arg 450					455			_	_	460				_
465	Asp			_	470		_		-	475	_			_	480
	Arg			485	_	_			490					495	
	Glu		500		_			505					510		
	Phe	515					520					525			
	Thr 530					535					540				
545	Ala				550					555					560
	Thr			565					570					575	
-	Phe		580			_		585					590		
	Lys	595					600					605	_		
	Leu 610	-				615					620		_		
Cys	Thr	His	Arg	Leu	Asp	Pro	Lys	Ser	Pro	Gly	Val	Asp	Arg	Glu	Gln

208

625 630 635 Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Gly Ile Lys Glu Leu Gly 645 650 Pro Tyr Thr Leu Asp Arg Xaa Ser Leu Tyr Val Asn Gly Phe Thr His 665 Trp Ile Pro Val Pro Thr Ser Ser Thr Pro Gly Thr Ser Thr Val Asp 680 Leu Gly Ser Gly Thr Pro Ser Ser Leu Pro Ser Pro Thr Thr Ala Gly 695 700 Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln 710 715 Tyr Glu Glu Asp Met His His Pro Gly Ser Arg Lys Phe Asn Thr Thr 725 730 735 Glu Arg Val Leu Gln Gly Leu Leu Gly Pro Met Phe Lys Asn Thr Ser 745 Val Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu 760 Lys Asn Gly Ala Ala Thr Gly Met Asp Ala Ile Cys Ser His Arg Leu 775 780 Asp Pro Lys Ser Pro Gly Leu Asn Arg Glu Gln Leu Tyr Trp Glu Leu 790 795 Ser Gln Leu Thr His Gly Ile Lys Glu Leu Gly Pro Tyr Thr Leu Asp 805 810 Arg His Ser Leu Tyr Val Asn Gly Phe Thr His Trp Ile Pro Val Pro 825 820 Thr Ser Ser Thr Pro Gly Thr Ser Thr Val Asp Leu Gly Ser Gly Thr 840 Pro Ser Ser Leu Pro Ser Pro Thr Thr Ala Gly Pro Leu Leu Val Pro 855 860 Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Xaa Tyr Glu Glu Asp Met 870 875 His Cys Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln 885 890 Ser Leu Leu Gly Pro Met Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr 900 905 Ser Gly Cys Arg Leu Thr Leu Leu Arg Ser Glu Lys Asp Gly Ala Ala 915 920 Thr Gly Val Asp Ala Ile Cys Thr His Arg Leu Asp Pro Lys Ser Pro 935 Gly Val Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn 950 955 Xaa Ile Lys Glu Leu Gly Pro Tyr Thr Leu Asp Ser Asn Ser Leu Tyr 965 970 Val Asn Gly Phe Thr His Gln Thr Ser Ala Pro Asn Thr Ser Thr Pro 980 985 Gly Thr Ser Thr Val Asp Leu Gly Xaa Ser Gly Thr Pro Ser Ser Leu 995 1000 1005 Pro Ser Pro Thr Ser Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn 1010 1015 1020 Phe Thr Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met His His Pro Gly 1030 1035 Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly \$1045\$ \$1050\$ \$1055\$ Pro Met Phe Lys Asn Thr Ser Val Gly Leu Leu Tyr Ser Gly Cys Arg 1065 1070 1060 Leu Thr Leu Leu Arg Pro Glu Lys Asn Gly Ala Ala Thr Gly Met Asp 1080 Ala Ile Cys Ser His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg

209

1095 1100 1090 Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Ile Lys Glu 1105 1110 1115 1120 Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn Gly Phe 1125 1130 1135 Thr His Arg Ser Ser Val Ala Pro Thr Ser Thr Pro Gly Thr Ser Thr 1140 1145 1150 Val Asp Leu Gly Thr Ser Gly Thr Pro Ser Ser Leu Pro Ser Pro Thr 1155 1160 1165 Thr Ala Val Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile Thr 1180 1175 Asn Leu Gln Tyr Gly Glu Asp Met Arg His Pro Gly Ser Arg Lys Phe 1190 1195 Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly Pro Leu Phe Lys 1205 1210 1215 Asn Ser Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Ile Ser Leu 1220 1225 1230 Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys Thr 1235 1240 1245 His His Leu Asn Pro Gln Ser Pro Gly Leu Asp Arg Glu Gln Leu Tyr 1250 1255 1260 Trp Gln Leu Ser Gln Met Thr Asn Gly Ile Lys Glu Leu Gly Pro Tyr 1270 1275 Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn Gly Phe Thr His Arg Ser 1285 1290 Ser Gly Leu Thr Thr Ser Thr Pro Trp Thr Ser Thr Val Asp Leu Gly 1300 1305 1310 Thr Ser Gly Thr Pro Ser Pro Val Pro Ser Pro Thr Thr Ala Gly Pro 1315 1320 1325 Leu Leu Val Pro Phe. Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr 1330 1335 1340 Glu Glu Asp Met His Arg Pro Gly Ser Arg Lys Phe Asn Ala Thr Glu 1350 1355 1360 Arg Val Leu Gln Gly Leu Leu Ser Pro Ile Phe Lys Asn Ser Ser Val 1365 1370 1375 Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Ser Leu Arg Pro Glu Lys 1380 1385 1390 Asp Gly Ala Ala Thr Gly Met Asp Ala Val Cys Leu Tyr His Pro Asn 1395 1400 1405 Pro Lys Arg Pro Gly Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser 1410 1415 1420 Gln Leu Thr His Asn Ile Thr Glu Leu Gly Pro Tyr Ser Leu Asp Arg 1425 1430 1435 1440 Xaa Ser Leu Tyr Val Asn Gly Phe Thr His Gln Asn Ser Val Pro Thr 1445 1450 1455 Thr Ser Thr Pro Gly Thr Ser Thr Val Tyr Trp Ala Thr Thr Gly Thr 1460 1465 1470 Pro Ser Ser Phe Pro Gly His Thr Glu Pro Gly Pro Leu Leu Ile Pro 1475 1480 1485 Phe Thr Phe Asn Phe Thr Ile Thr Asn Leu His Tyr Glu Glu Asn Met 1490 1495 1500 Gln His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln 1510 1515 Gly Leu Leu Thr Pro Leu Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr 1525 1530 Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys Gln Glu Ala Ala 1540 1545

Thr Gly Xaa Asp Thr Ile Cys Xaa His Arg Xaa Asp Pro Ile Gly Pro

		1555	5				1560)				1565	5		
Gly	Leu 1570	Asp		Glu	Xaa	Leu 1575	Tyr		Glu	Leu	Ser 1580		Leu	Thr	His
Xaa 1585		Thr	Glu	Leu	Gly 1590		Tyr	Thr	Leu	Asp 1595		Asp	Ser	Leu	Tyr 1600
Val	Asn	Gly	Phe	Asn 1605		Trp	Ser	Ser	Val 1610		Thr	Thr	Ser	Thr 1615	
Gly	Thr	Ser	Thr 1620	Val	His	Leu	Ala	Thr 1625		Gly	Thr	Pro	Ser 1630		Leu
Pro	Gly	His 1635		Ala	Pro	Val	Pro 1640		Leu	Ile	Pro	Phe 1645		Leu	Asn
Phe	Thr 1650		Thr	Asn	Leu	His 1655	Tyr	Glu	Glu	Asn	Met 166		His	Pro	Gly
Ser 1669		Lys	Phe	Asn	Thr 1670		Glu	Arg	Val	Leu 1679		Gly	Leu	Leu	Lys 1680
•			_	Ser 1685	5			_	1690)	-		_	1695	5
			1700	_				1705	õ				1710)	
		1715	5	Leu			1720)				1725	5		
	1730	ο.		Trp		1739	5				174	0			
1745	5			Thr	1750)				175	5				1760
				Ser 1769	5				1770)				177	5
			1780			_		178	5				1790	כ	
		179	5	Leu			1800)				180	5		
	1810) · C		Glu		1819	5				182	0			
182	5			Arg	1830)				183	5				1840
				Gly 1845	5				1850	0				185	5
			186	-				1869	5				1870)	
	_	187	5	Pro			1880)		-	•	1889	5		-
	1890)		Lys		189	5				190	0			
190	5	_	_		1910)				191	5				Asn 1920
				Thr 192	5			_	1930	0				193	5
			194					194	5				195	0	
		195	5	Phe			1960)				196	5		_
	1970)		Arg		1975	5		-	_	198	0			
198	5			Gly	1990)				199	5				2000
			_	Ser 200	5				2010	0				201	5
Asp	Lys	Ala	Ala	Thr	Arg	Val	Asp	Ala	Ile	Cys	Thr	His	His	Pro	Asp

211

2020 2025 2030 Pro Gln Ser Pro Gly Leu Asn Arg Glu Gln Leu Tyr Trp Glu Leu Ser 2035 2040 2045 Gln Leu Thr His Gly Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg 2050 2055 2060 Xaa Ser Leu Tyr Val Xaa Gly Phe Thr His Trp Ser Pro Ile Pro Thr 2070 2075 2080 Thr Ser Thr Pro Gly Thr Ser Ile Val Asn Leu Gly Thr Ser Gly Ile 2085 2090 2095 Pro Pro Ser Leu Pro Glu Thr Thr Ala Thr Gly Pro Leu Leu Val Pro 2100 2105 Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr Glu Glu Asn Met 2115 2120 2125 Gly His Pro Gly Ser Arg Lys Phe Asn Ile Thr Glu Ser Val Leu Gln 2130 2135 2140 Gly Leu Leu Lys Pro Leu Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr 2145 2150 2155 2160 Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Val Ala 2165 2170 2175 Thr Arg Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Lys Ile Pro 2180 2185 2190 Gly Leu Asp Arg Gln Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His 2195 2200 2205 Ser Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr 2210 2215 2220 Val Asn Gly Phe Thr Gln Arg Ser Ser Val Pro Thr Thr Ser Thr Pro 2225 2230 2235 2240 Gly Thr Phe Thr Val Gln Pro Glu Thr Ser Glu Thr Pro Ser Ser Leu 2245 2250 2255 Pro Gly Pro Thr Ala Thr Gly Pro Val Leu Leu Pro Phe Thr Leu Asn 2260 2265 2270 Phe Thr Ile Ile Asn Leu Gln Tyr Glu Glu Asp Met His Arg Pro Gly 2275 2280 2285 Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Met 2290 2295 2300 Pro Leu Phe Lys Asn Thr Ser Val Ser Ser Leu Tyr Ser Gly Cys Arg 2305 2310 2315 2320 Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Arg Val Asp 2325 . 2330 2335 Ala Val Cys Thr His Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp Arg 2340 2345 2350 Glu Arg Leu Tyr Trp Lys Leu Ser Gln Leu Thr His Gly Ile Thr Glu 2355 2360 2365 Leu Gly Pro Tyr Thr Leu Asp Arg His Ser Leu Tyr Val Asn Gly Phe 2370 2375 2380 Thr His Gln Ser Ser Met Thr Thr Thr Arg Thr Pro Asp Thr Ser Thr 2385 2390 2395 2400 Met His Leu Ala Thr Ser Arg Thr Pro Ala Ser Leu Ser Gly Pro Thr 2405 2410 2415 Thr Ala Ser Pro Leu Leu Val Leu Phe Thr Ile Asn Phe Thr Ile Thr 2425 2430 Asn Leu Arg Tyr Glu Glu Asn Met His His Pro Gly Ser Arg Lys Phe 2435 2440 2445 Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Val Phe Lys 2450 2455 2460 Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu 2470 2475 2480 Arg Pro Lys Lys Asp Gly Ala Ala Thr Lys Val Asp Ala Ile Cys Thr

		2485				2490	2				2495	5
Tyr Arg F	ro Asp	Pro Lys	Ser	Pro	Gly 2505	Leu		Arg			Leu	
Trp Glu I	eu Ser	_	Thr		Ser		Thr	Glu		Gly		Tyr
Thr Leu A	2515 Asp Arg	Asp Ser				Asn	Gly				Arg	Ser
2530 Ser Val E	ro Thr				Gly	Thr	Pro 2555		-	Asp	Leu	
2545 Thr Ser (Sly Thr			Lys	Pro		Pro		Ala	Ala		
Leu Leu \			Leu	Asn	Phe 2585			Thr	Asn	Leu 259	_	
Glu Glu A	258 Asn Met 2595		Pro	Gly 2600	Ser		Lys	Phe	Asn 260	Thr	-	Glu
Arg Val I 2610		Gly Leu	Leu 261	Arg		Leu	Phe	Lys 262	Ser		Ser	Val
Gly Pro I 2625	eu Tyr	Ser Gly 263	Cys		Leu		Leu 2635	Leu		Pro	Glu	
Asp Gly	hr Ala			Asp	Ala		Cys		His	His	Pro 265	
Pro Lys S	Ser Pro 266	Arg Leu	Asp	Arg	Glu 266	Gln	-	Tyr	Trp	Glu 267	Leu	
Gln Leu 1			Thr	Glu 2680	Leu		Xaa	Tyr	Ala 268	Leu		Asn
Asp Ser I		Val Asn	Gly 269	Phe		His	Arg	Ser 270	Ser		Ser	Thr
Thr Ser 7	Thr Pro	Gly Thr	Pro		Val	Tyr	Leu 271	Gly		Ser	Lys	Thr 2720
Pro Ala S	Ser Ile		_	Ser	Ala	Ala 273	Ser		Leu	Leu	Ile 273	Leu
Phe Thr I	Leu Asn 274	Phe Thr	Ile	Thr	Asn 274	Leu		Tyr	Glu	Glu 275	Asn	
Trp Pro (-	Phe	Asn 276	Thr		Glu	Arg	Val 276	Leu		Gly
Leu Leu 2 2770		Leu Phe	Lys 277	Asn		Ser	Val	Gly 278	Pro	-	Tyr	Ser
Gly Cys 2 2785	Arg Leu	Thr Leu 279	Leu		Pro	Glu	Lys 279		Gly	Glu	Ala	Thr 2800
Gly Val A	Asp Ala			His	Arg	Pro 281	-	Pro	Thr	Gly	Pro 281	_
Leu Asp A	Arg Glu 282		_				Ser			Thr 283		Ser
Ile Thr	Slu Leu 2835	Gly Pro	Tyr	Thr 2840		Asp	Arg	Asp	Ser 284		Tyr	Val
Asn Gly I 2850	he Thr	His Arg	Ser 285		Val	Pro	Thr	Thr 286		Thr	Gly	Val
Val Ser (2865	Slu Glu	Pro Phe 287		Leu	Asn	Phe	Thr 2879		Asn	Asn	Leu	Arg 2880
Tyr Met A	Ala Asp	Met Gly 2885	Gln	Pro	Gly	Ser 289		Lys	Phe	Asn	Ile 289	
Asp Asn V	/al Met 290		Leu	Leu	Ser 290		Leu	Phe	Gln	Arg 291		Ser
	915			292	0				292	5		
Lys Asn (2930	Sly Ala	Glu Thr	Arg 293		Asp	Leu	Leu	Cys 294		Tyr	Leu	Gln
Pro Leu S	Ser Gly	Pro Gly	Leu	Pro	Ile	Lys	Gln	Val	Phe	His	Glu	Leu

213

2955 2945 2950 Ser Gln Gln Thr His Gly Ile Thr Arg Leu Gly Pro Tyr Ser Leu Asp 2965 2970 2975 Lys Asp Ser Leu Tyr Leu Asn Gly Tyr Asn Glu Pro Gly Xaa Asp Glu 2980 2985 2990 Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr Phe Leu Pro Pro Leu Ser 2995 3000 3005 Glu Ala Thr Thr Ala Met Gly Tyr His Leu Lys Thr Leu Thr Leu Asn 3010 3015 · 3020 Phe Thr Ile Ser Asn Leu Gln Tyr Ser Pro Asp Met Gly Lys Gly Ser 3030 3035 Ala Thr Phe Asn Ser Thr Glu Gly Val Leu Gln His Leu Leu Arg Pro 3045 3050 3055 Leu Phe Gln Lys Ser Ser Met Gly Pro Phe Tyr Leu Gly Cys Gln Leu 3060 3065 3070 Ile Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Thr 3075 3080 3085 Thr Cys Thr Tyr His Pro Asp Pro Val Gly Pro Gly Leu Asp Ile Gln 3100 3090 3095 Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Val Thr Gln Leu 3110 3115 Gly Phe Tyr Val Leu Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr Ala 3125 3130 Pro Gln Asn Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn Phe His Ile 3140 3145 3150 Val Asn Trp Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser Glu Tyr Ile 3155 3160 3165 Thr Leu Leu Arg Asp Ile Gln Asp Lys Val Thr Thr Leu Tyr Lys Gly 3170 3175 3180 Ser Gln Leu His Asp Thr Phe Arg Phe Cys Leu Val Thr Asn Leu Thr 3185 3190 3195 3200 Met Asp Ser Val Leu Val Thr Val Lys Ala Leu Phe Ser Ser Asn Leu 3210 3215 3205 Asp Pro Ser Leu Val Glu Gln Val Phe Leu Asp Lys Thr Leu Asn Ala 3220 3225 Ser Phe His Trp Leu Gly Ser Thr Tyr Gln Leu Val Asp Ile His Val 3235 3240 3245 Thr Glu Met Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser Ser Ser Thr 3250 3255 3260 Gln His Phe Tyr Xaa Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser Gln 3265 3270 3275 3280 Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg Asn 3285 3290 3295 Ile Glu Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys Ser 3300 3305 Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn Arg 3315 3320 3325 His His Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala Arg 3330 3335 3340 Arg Val Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr Arg 3350 3355 3360 Asn Gly Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val Leu 3365 3370 Val Asp Gly Tyr Xaa Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn Ser 3380 3385 Asp Leu Pro Phe Trp Ala Val Ile Xaa Ile Gly Leu Ala Gly Leu Leu 3395 3400 3405 Gly Leu Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr Arg Arg

214

3410 3415 3420

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3425 3430 3435 3440

Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln

3445 3450

<210> 596

<211> 156

<212> PRT

<213> Homo sapiens

<400> 596

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5 10 15

Ser Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Ser Ser Leu Pro Ser 20 25 30

Pro Thr Ala Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met His His Pro Gly Ser Arg
50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Gln
115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

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[Continued on next page]

(54) Title: COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF OVARIAN CANCER

17 July 2001 (17.07.2001)

11729.1 contg

11729-45.21.21.cons1

TAGGATGTGTIGGACCCTCTGTGTCAAAAAAAACCTCACAAAGAATCCCCTGCTCATTACAGAAGAAGATGCAT
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CTTTGATGACAGTAAAAATGGCCTTTCTGCATGGGAACTTATTGGACTTATTGGAAATGGACAGTTTAACAACAG
GCATGGACCGGCAGACTGTGTCTATGGCAATTAATGAAGTCTTTAATGAACTTAATTAGATGTGTTAAAGCAG
GGTTACATGATGAAAAAGGGCCCACAGACGGAAAAACTGGACTGAAAGATGGTTTGATAAAACCCAACATTAAT
TTCTTTACTATGTGAGGTACTGAAGGATAAGAAAGGAGAACATTCTCTTGGATGAAAATTGCTGTGTAGAGT
CCTTGCCTGACAAAGATGGAAA

11729-45.21.21.cons2

11731.lcontig

(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as ovarian cancer, are disclosed. Compositions may comprise one or more ovarian carcinoma proteins, immunogenic portions thereof, polynucleotides that encode such portions or antibodies or immune system cells specific for such proteins. Such compositions may be used, for example, for the prevention and treatment of diseases such as ovarian cancer. Methods are further provided for identifying tumor antigens that are secreted from ovarian carcinomas and/or other tumors. Polypeptides and polynucleotides as provided herein may further be used for the diagnosis and monitoring of ovarian cancer.



WO 02/006317 A3



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- (74) Agents: POTTER, Jane, E., R.; Seed Intellectual Property Law Group PLLC, Suite 6300, 701 Fifth Avenue, Seattle, WA 98104-7092 et al. (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

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- (88) Date of publication of the international search report: 3 July 2003

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INTERNATIONAL SEARCH REPORT

stional Application No

			PU1/US 01	/22635
	FICATION OF SUBJECT MATTER C07K14/47 C12N15/12 C12N15/ G01N33/574 C12Q1/68 C12N15/ A61K39/395	/62 C12N5/0		16/30 39/00
	b International Patent Classification (IPC) or to both national classification	cation and IPC		
	ocumentation searched (classification system followed by classification	tion symbols)		
Documenta	lon searched other than minimum documentation to the extent that	such documents are inclu	ded in the fields se	arched
	ata base consulted during the international search (name of data b ternal, WPI Data, PAJ, BIOSIS, MEDI		search terms used)	
C. DOCUM	ENTS CONSIDERED TO BE RELEVANT			
Category *	Citation of document, with indication, where appropriate, of the re	elevant passages		Relevant to claim No.
X	WO 00 36107 A (CORIXA CORP) 22 June 2000 (2000-06-22)	-1: 0770D	,	1-3,7, 15, 19-32,35
	SEQ ID NO:311, 312, 385-390 enco polynucleotides and polypeptides pages 48, 50, 51 claims 1,2,7,8,13-17,21,33,37,3	5		
Α	SCHUMMER MICHEL ET AL: "Compara hybridization of an array of 21 ovarian cDNAs for the discovery overexpressed in ovarian carcino GENE (AMSTERDAM), vol. 238, no. 2, 1 October 1999 (1999-10-01), pag 375-385, XP002222131 ISSN: 0378-1119	1,7,24, 25,32		
	the whole document			
Furth	er documents are listed in the continuation of box C.	X Patent family r	nembers are listed i	n annex.
"A" docume conside "E" earlier difiling de "L" documee which i citation "O" docume other n "P" docume	nt which may throw doubts on priority claim(s) or s cited to establish the publication date of another or other special reason (as specified) nt referring to an oral disclosure, use, exhibition or	cited to understan invention "X" document of partice cannot be conside involve an invention "Y" document of partice cannot be conside document is comb	I not in conflict with d the principle or the ilar relevance; the c red novel or cannot re step when the do ilar relevance; the c tred to involve an im dined with one or mo dination being obvious	the application but every underlying the laimed invention be considered to cument is taken alone laimed invention ventive step when the re other such docu- us to a person skilled
Date of the a	ctual completion of the international search	Date of mailing of t	he International sea	rch report
1:	l December 2002	01 04	2003	
Name and m	alling address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk	Authorized officer		
	Tel. (+31-70) 340-2040, Tx. 31.651 epo nl, Fax: (+31-70) 340-3018	Brouns,	. G	

INTERNATIONAL SEARCH REPORT

Iternational application No. PCT/US 01/22635

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely: see FURTHER INFORMATION sheet PCT/ISA/210
2. X Claims Nos.:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple Inventions in this international application, as follows:
see additional sheet
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-3, 7, 15, 19-32, 35 all partially
Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

Continuation of Box I.1

Although claims 25 and 32 are directed to a diagnostic method practised on the human or animal body, the search has been carried out and based on the alleged effects of the compostion.

Although claims 27, 30 and 31 are directed to a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects of the composition.

Continuation of Box I.2

Present claims 1-11 and 15-19 relate to an extremely large number of possible compounds. In fact, the claims contain so many options for an ovarian carcinoma antigen 0772P that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise.

In view of the description (page 5, line 28-page 6, line 5), an 0772P consensus repeat sequence 'X' as set forth in SEQ ID NO:596 is considered to be a sequence element of 156 amino acids. As a consequence, the search has been limited to an 0772P polypeptide comprising an X repeat 'consisting' of a sequence as defined by the claimed SEQ ID NOs in the application.

Present claim 25 relates to an agent defined by reference to a desirable characteristic or property, namely that it binds to a polypeptide of claim 21.

The claim covers all agents having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such agents. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the agents by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to antibodies binding to a polypeptide of claim 21.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-3,7,15,19-32,35, all partially

Invention 1

An 0772P polypeptide having the structure X-Y, wherein X comprises the sequence defined by SEQ ID NO:574 and Y comprises a sequence having at least 80% identity with the sequence of SEQ ID NO:594, a polynucleotide encoding said X repeat defined by SEQ ID NO:542, said polypeptide or polynucleotide being overexpressed in ovarian cancer cells compared with normal tissue, an isolated nucleic acid sequence defined by SEQ ID NO:542, complement thereof, sequence containing at least 20 contiguous residues thereof, sequences that hybridise to said sequence, sequence having at least 75% or 90% identity to said sequence, degenerate variants of said sequence, polypeptides encoded by said sequence, said sequence in an expression vector, a host cell transfected with said expression vector, an isolated antibody binding aforementioned polypeptide, a method of diagnosing cancer using said peptide, a fusion protein comprising said peptide, a method for stimulating or expanding T cells using said polynucleotides or polypeptides and the resulting T cell population, a composition comprising said polynucleotide, polypeptide, antibody, fusion protein, T cell population or antigen presenting cells expressing the polypeptide, a method for stimulating an immune response, a method for treatment of ovarian cancer, a method of determining ovarian cancer in a patient and an antibody against the specific 0772P polypeptide of the invention.

2. Claims: 1-3,7,35, all partially

Inventions 2-20

As for invention 1, but limited to subject-matter relating to polypeptides having an X domain as defined in SEQ ID NO: 575-593, whereby invention 2 is limited to SEQ ID NO:575, invention 3 is limited to SEQ ID NO:576, invention 4 is limited to SEQ IS NO:577, etc..., invention 19 is limited to SEQ ID NO:592 and invention 20 is limited to SEQ ID NO:593

3. Claims: 15 and 19-32, all partially

Invention 21

A polynucleotide encoding an 0772P polypeptide having the structure X-Y, whereby X and Y are encoded by the sequence defined by SEQ ID NO:512 and SEQ ID NO:568, respectively, said polypeptide overexpressed in ovarian cancer cells

compared with normal tissue and an isolated nucleic acid sequence defined by SEQ ID NO:512, complement thereof. sequence containing at least 20 contiguous residues thereof. sequences that hybridise to said sequence, sequence having at least 75% or 90% identity to said sequence, degenerate variants of said sequence, polypeptides encoded by said sequence, said sequence in an expression vector, a host cell transfected with said expression vector, an isolated antibody binding aforementioned polypeptide, a method of diagnosing cancer using said peptide, a fusion protein comprising said peptide, a method for stimulating or expanding T cells using said polynucleotides or polypeptides and the resulting T cell population, a composition comprising said polynucleotide, polypeptide, antibody, fusion protein, T cell population or antigen presenting cells expressing the polypeptide, a method for stimulating an immune response, a method for treatment of ovarian cancer and a method of determining ovarian cancer in a patient.

4. Claims: 15 and 19-32, all partially

Inventions 22-73

As for invention 21, but limited to the subject-matter relating to an X domain encoding polynucleotide as defined in SEQ ID NOs:513-540, 543-546 and 548-567, whereby invention 22 is limited to SEQ ID NO:513, invention 23 is limited to SEQ ID NO:514, invention 24 is limited to SEQ ID NO:540, invention 50 is limited to SEQ ID NO:543, invention 51 is limited to SEQ ID NO:544, invention 52 is limited to SEQ ID NO:545, invention 53 is limited to SEQ ID NO:546, invention 54 is limited to SEQ ID NO:548, invention 55 is limited to SEQ ID NO:549, ..., invention 72 is limited to SEQ ID NO:566 and invention 73 is limited to SEQ ID NO:567

5. Claims: 20-32, all partially

Invention 74

Isolated nucleic acid sequence defined by SEQ ID NO:464, complement thereof, sequence containing at least 20 contiguous residues thereof, sequences that hybridise to said sequence, sequence having at least 75% or 90% identity to said sequence, degenerate variants of said sequence, polypeptides encoded by said sequence, said sequence in an expression vector, a host cell transfected with said expression vector, an isolated antibody binding aforementioned polypeptide, a method of diagnosing cancer using said peptide, a fusion protein comprising said peptide, a method for stimulating or expanding T cells using said polynucleotides or polypeptides and the resulting T cell population, a composition comprising said

polynucleotide, polypeptide, antibody, fusion protein, T cell population or antigen presenting cells expressing the polypeptide, a method for stimulating an immune response, a method for treatment of ovarian cancer and a method of determining ovarian cancer in a patient.

6. Claims: 20-32, all partially

Inventions 75-91

As for invention 74, but limited to the subject-matter relating to an nucleic acid sequence as defined in SEQ ID NOs:465-477, 541, 547, 568 and 569, wherein invention 75 is limited to SEQ ID NO:465, invention 76 is limited to SEQ ID NO:466, invention 77 is limited to SEQ ID NO:467, invention 78 is limited to SEQ ID NO:468, invention 79 is limited to SEQ ID NO:469, invention 80 is limited to SEQ ID NO:470, invention 81 is limited to SEQ ID NO:471, invention 82 is limited to SEQ ID NO:472, invention 83 is limited to SEQ ID NO:473, invention 84 is limited to SEQ ID NO:474, invention 85 is limited to SEQ ID NO:475, invention 86 is limited to SEQ ID NO:476, invention 87 is limited to SEQ ID NO:477, invention 88 is limited to SEQ ID NO:541, invention 89 is limited to SEQ ID NO:568, invention 91 is limited to SEO ID NO:569

7. Claims: 33, partially

Invention 92

An 0772P polypeptide comprising at least an antibody epitope sequence set forth in SEQ ID NO:490

8. Claims: 33, partially

Inventions 93-113

As for invention 92, but limited to the subject-matter relating to an antibody epitope as defined in SEQ ID NO:491-511, wherein invention 93 is limited to SEQ ID NO:491, invention 94 is limited to SEQ ID NO:492, ..., invention 113 is limited to SEQ ID NO:511

9. Claims: 34, partially

Invention 114

An O8E polypeptide comprising at least an antibody epitope sequence set forth in SEQ ID NO:394

10. Claims: 34, partially

Inventions 115-135

As for invention 114, but limited to the subject-matter relating to an antibody epitope as defined in SEQ ID NOs:395-415, wherein invention 115 is limited to SEQ ID NO:395, invention 116 is limited to SEQ ID NO:396, ..., invention 135 is limited to SEQ ID NO:415

INTERNATIONAL SEARCH REPORT

Information on patent family members

tonal Application No
PCT/US 01/22635

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